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NEUROSURGICAL TREATMENT OF DISORDERS OF THE AFFECT

J. LAWRENCE POOL, M.D.*

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BRAIN surgery for the treatment of disorders of the affect has now been tested for more than fifteen years and is often referred to as psychosurgery.[1] A basic principle of most of the procedures used for this purpose, particularly those involving frontal lobe surgery, appears to be reduction of the tension or anxiety that underlies so many of the chronic psychoses, neuroses, and depressions. Interruption of thalamofrontal connections, notably those between the dorsomedian thalamic nuclei and the frontal cortex, is thought to be a major factor in the reduction of this abnormal emotional charge or anxiety. It must be borne in mind, however, that in many of these operations other important pathways may also be interrupted such as those linking the frontal gray matter directly or indirectly with parts of the thalamus, hypothalamus, basal ganglia, brain stem, and the temporal, occipital, and parietal lobes.

The obvious aim of the various procedures under discussion is to achieve maximal therapeutic effectiveness with minimal manipulative risks. Therapeutic effectiveness seems to depend largely on the amount or quantity of frontal lobe disconnection rather than on the actual location of the lesion,[2,3] although the latter point is still a subject of dispute. In other words, frontal lobe and related neural functions must be interfered with to an adequate or critical degree for a given patient or condition in order to induce lasting relief of symptoms.

*Professor of Neurological Surgery, Columbia University; and Director, Service of Neurological Surgery, Columbia Presbyterian Medical Center, New York, N. Y.

Severe chronic psychoses, for example, may require a more extensive procedure from the quantitative standpoint than do chronic neuroses or depressions. Too great a sacrifice of cerebral function by any of these procedures, on the other hand, generally leads to impairment of intellectual and emotional capacities that is roughly proportional to the magnitude of the surgical lesion. Intelligence, emotional responses and drive, however, are not seriously or even appreciably affected in many cases treated by the more precise and quantitatively more conservative techniques that have been used in the last six or seven years. It is true that residual disturbances in the intellectual and emotional spheres may be apparent after the postoperative disappearance of delusions, hallucinations, agitated states, and so on, in severe psychotic patients. However, these persisting deficits generally reflect some degree of continued physiologic or psychodynamic dysfunction that is attributable to the original psychotic process rather than to the effects of the operation itself.

Manipulative risk refers to the chances of short- and long-term postoperative complications secondary to the extent, location, or actual technique of a given procedure.

A. Short-term, more or less immediate postoperative, complications include death, hemorrhage, cerebral edema, infection, convulsions, profound apathy, incontinence, and hemiplegia. None of these complications, however, occurs with any significant frequency following the various procedures in current use, although they used to be more frequent some years ago following the radical lobotomies that are now practically obsolete. For example, there has not been a single instance of operative death, intracranial hemorrhage, massive edema, infection, or other serious complication in the author's series of more than one hundred topectomy or cortical ablation operations and more than fifty prefrontal lobotomy procedures during the past six and one half years. Following prefrontal and transorbital lobotomies[4] and allied procedures in larger series the incidence of operative fatality is about 3 per cent, hemorrhage about 1 per cent, and infection less than half of 1 per cent. Hemiplegia has only rarely occurred following a lobotomy. Urinary and occasional fecal incontinence may occur in about one-fourth of the patients during the first day or so after most of the frontal lobe operations to be described, with the exception of transorbital lobotomy which is seldom extensive enough to result in such an effect. Seizures are rare in the immediate postoperative course after almost all of the procedures. Indeed, the majority of patients after prefrontal lobotomy or topectomy are up and about the day following their operation, already indulging in three meals a day, and are able to read, converse, and greet their friends and family, despite an element of vagueness that usually disappears after a week or so. Following a transorbital lobotomy most patients become ambulatory as soon as they recover from electroshock or anesthesia unconsciousness.

The usual period of convalescence in the hospital is a week or ten days. During this time, or for a longer period in some cases, there may be a temporary accentuation of psychotic behavior sometimes described as an echo phenomenon. Frequently this appears to indicate a favorable progress. After discharge from the hospital a period of convalescence in a private or public institution is gener-

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ally required for six weeks to six months, for purposes of psychiatric rather than physical rehabilitation and re-education.

B. Long-term complications such as persisting apathy or incontinence have rarely been seen in recent years. There is no serious diminution of drive and of normal emotional responses, nor impairment of higher mental faculties such as abstract thinking and foresight unless too radical an operation has been performed or unless the original disease is too far advanced to be greatly improved by surgery. In the most successfully treated patients there is usually excellent preservation of drive and planning and learning ability that has actually led to promotions and greater success in business than was possible before overt symptoms began. Moreover, emotional qualities are also maintained or restored to a relatively normal degree by operation in such cases, as manifested by personal reactions, stability, affection for family, successful marriages, and pregnancies without postpartum psychic disturbances.

After some of these procedures there may be postoperative seizures, but they are usually few in number. Among the predisposing factors that may lead to such seizures are preoperative cerebral abnormalities as revealed by electroencephalography or a history of seizures even in childhood[3]; a second brain operation (which may raise the seizure incidence to over 40 per cent)[1]; and excessive cerebral trauma at operation. According to the writer's experience, the greater the proximity of an operative incision to the motor cortex, the higher may be the postoperative seizure incidence.[3] If seizures do occur, it is rare that there is more than one a year, unless there has been evidence of preoperative seizure predisposition or two operations have been done. The tendency to seizure occurrence furthermore is usually reduced by the use of appropriate anticonvulsant medication such as Dilantin sodium 0.1 Gm. three times a day, which may be routinely prescribed following some of these procedures as a precautionary measure. In figuring the seizure incidence most writers count every patient who has had a postoperative convulsion, even though only one has occurred in the immediate postoperative period. On the basis of these explanatory remarks it can be seen that the seizure problem may not necessarily be as serious as the figures might suggest.

While Freeman and Watts[1] originally reported a postlobotomy seizure incidence in the neighborhood of 10 per cent, Freeman[4] has had the opportunity of a more recent survey and reports an incidence of about 25 per cent following prefrontal or frontal lobotomy. In one unpublished series of fifty lobotomies of which the writer is aware, a 50 per cent seizure incidence occurred. Others, however, such as Poppen,[5] Scoville,[6] and the author have found that considerably less than 10 per cent of their lobotomy cases suffered one or more seizures. Some of the disparity between these figures may be due to variations in operative techniques, especially with the earlier procedures that often led to more operative injury to the brain than present ones. Following transorbital lobotomy the seizure incidence is thus far less than 3 per cent.[4] After bilateral topical ablation of cerebral cortex (topectomy)[3] from various parts of the frontal lobes, the over-all seizure incidence has been approximately 15 per cent. For one state hospital study of a few severely deteriorated schizophrenic cases some

years ago, the motor cortex was exposed for purposes of orientation and special observation. This led to a seizure incidence of over 25 per cent. However during the past six and one half years when the cortical ablation was confined to the anterior extent or pole of the frontal lobes and the adjacent medial and orbital gyri,[7] in what is called a polar topectomy, the seizure incidence has been reduced to less than 7 per cent and thus compares favorably with lobotomy statistics. As stated above, this total experience with cortical ablations lends support to the impression that the postoperative seizure incidence is significantly lower when the surgical procedure is more remote from the motor cortex.

Before describing various procedures, certain broad principles with reference to psychosurgery deserve attention. First, this type of brain surgery should not be done for the alleviation of mental or emotional illnesses without the recommendation of a competent psychiatrist who is familiar with the proposed procedure.

Second, psychosurgery should obviously not be advised until all other appropriate therapeutic measures such as psychotherapy, drug therapy, and shock treatment have been given a fair trial.

Third, it should be explained to the patient whenever feasible, and certainly to the family or guardian, that brain surgery (a) may not relieve the condition and (b) may lead to complications such as epileptiform convulsions, adverse personality changes, incontinence, paralysis, or even death, although these are not likely to occur following the less radical operative procedures currently used.

Fourth, the type of operation selected should be carefully considered with respect to the nature of the malady, the age and physical state of the patient, and the experience of the operator with a given procedure.

Finally, postoperative support from the psychiatrist and particularly the family is most important.

OPERATIVE PROCEDURES

Lobotomy.—Lobotomy or leukotomy[1] means section of the white matter of a lobe of the brain. A *prefrontal* lobotomy is carried out anterior to the premotor cortex and is called a *precoronal* lobotomy when done anterior to the coronal suture, as is currently the custom. When the section is limited to the medial fibers of each frontal lobe, the procedure is called a *bimedial* prefrontal lobotomy. Otherwise section of the lateral as well as the medial half of the frontal white matter is implied. Lobotomy may be performed by a closed or open method, and the fibers may be destroyed by a cutting spatula (Fig. 1), a leukotome, a small suction tube, the injection of alcohol or even Novocain, by a coagulating (Grantham) needle,[8] by controlled ultrasonic irradiation,[9] or by implantation of radioactive seeds.

Before making a lobotomy incision it is customary to determine the anterior extent of the lateral ventricle and the distance from the presenting cortical surface of the floor of the anterior fossa by preliminary exploration with the

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ventricular needle. In this way the white matter can be more accurately sectioned or destroyed without great risk of entering the ventricles or ripping a blood vessel in the depths of the incision.

The closed type of lobotomy may be done through a 1 inch incision on each side of the midline where small burr holes permit dural opening and a small 3 to 4 mm. transcortical incision. Following the lobotomy a silver clip or some other marker may be inserted in the depths of each incision, and finally a metal disc or the like may be placed over each burr opening before closure of the scalp, to preserve the natural contour. The entire procedure usually takes an hour or less.

Open lobotomy and "undercutting"[6] (which is essentially a lobotomy incision parallel to the depths of the gray matter) may be done with a large 1½ inch drill[5] or a small craniotomy bone flap,[10] visualization of the depths of the white matter being accomplished by retractors through a cortical incision 2 to 3 cm. in length. Otherwise the procedure is essentially the same as for the closed type of operation.

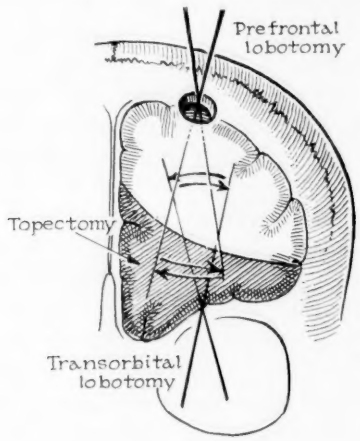
Transorbital Lobotomy.—Transorbital lobotomy[4,11,12,13] in experienced hands appears to be a simple and surprisingly safe procedure, and is usually carried out with the patient rendered unconscious by electric shock or by intravenous Pentothal sodium. A graduated spikelike instrument is inserted above the eyeball, tapped through the thin roof of the orbit into the relatively avascular cerebral portion of the subfrontal cortex and then introduced measured distances into the white matter where it is moved so as to cut the white matter at two or three planes (Fig. 1). The whole procedure requires no more than a few minutes time for each side and the patient promptly regains consciousness. Nosik[14] describes a leukotome used for this procedure under x-ray guidance.

Closed lobotomy is a somewhat simpler procedure than open lobotomy though both types can be easily and briefly performed under local anesthesia in some patients. Effects can thus be evaluated while the patient is on the operating table, enabling the surgeon to proceed until the desired effect is obtained. The brief time required and the fact that general anesthesia is not always necessary make the closed procedure highly desirable for older or debilitated patients, particularly those with advanced carcinomatosis in whom postoperative pulmonary complications are otherwise apt to occur.

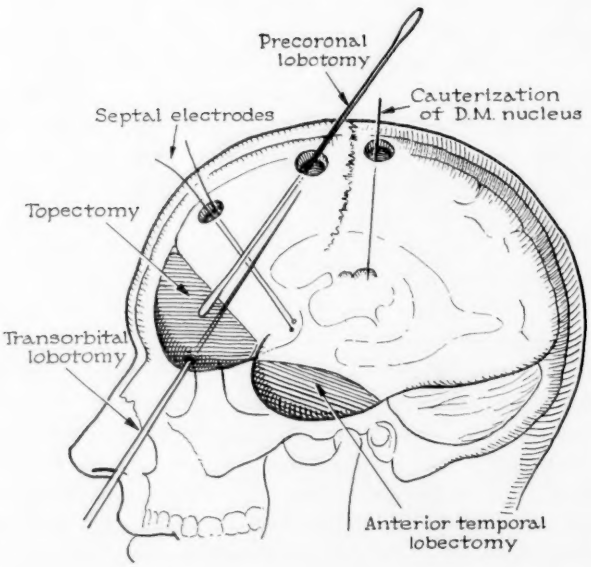
In the closed type of lobotomy, however, the precise direction and extent of the lobotomy incision cannot be judged as well as by open methods that permit better visualization. By the same token deep blood vessels may be injured with subsequent postoperative hemorrhage. For these reasons the author feels it unsafe to attempt by a closed lobotomy as radical or extensive a procedure as might be indicated for relief of severe psychotic states such as advanced schizophrenia.

While open lobotomies allow the neurosurgeon to visualize the path of his lobotomy incision and achieve satisfactory hemostasis, they require a rather wide transcortical incision and considerable retraction of brain tissue which may result in a higher incidence of postoperative seizures.

Unilateral lobotomy,[10] in my experience, does not usually stand the test of time, being effective as a rule for only three to six weeks. It is therefore advisable mostly for pain relief in preterminal cases of carcinomatosis.



A.



B.

Fig. 1.—*A* and *B*, Diagrams showing approximate location and extent of procedures described in text in sagittal and cross section views.

I do not regard with enthusiasm the use of the electrocoagulating or Grantham needle[8] for lobotomy, as the extent of the coagulation is not always predictable. Grantham and Spurling,[8] however, obtained excellent results with this technique.

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Transorbital lobotomy is obviously the simplest of all these procedures. While infections are so rare as to be negligible, fatal postoperative hemorrhages have occurred in 1.2 per cent of the patients so operated upon.[4] Since several transorbital lobotomies may be done in the space of a few hours, this procedure has been used extensively and with considerable success in state hospitals where time and expense are such important factors. It is virtually impossible, however, to obtain as extensive a lobotomy by this means as by an open lobotomy or topectomy, so that patients requiring more extensive frontal lobe surgery have frequently required a second operation.[3] This may well be an advantage of the procedure in serving as a test of the efficacy of a conservative operation before resorting to a more radical operation.

Another distinct advantage of transorbital lobotomy is the very low incidence of postoperative seizures (1.6 per cent). In some hands, however, this procedure has not led to lasting improvement in many overt and "pseudoneurotic" schizophrenic cases. Hence a final evaluation on a statistical basis does not seem justifiable until even more figures than those already given[4,11,12,13] are reported from the various state hospitals and private clinics where transorbital lobotomies have been done on a large scale.

Cingulate Gyrus Lobotomy or Gyrectomy.[2,15,16]—This procedure has been used extensively and may be done through large burr holes or by means of a craniotomy flap.

Parietal Lobotomy.—Parietal lobotomy, designed to interrupt the affected sensory association pathways, has proved highly successful for the relief of a phantom limb syndrome without creating personality deficits.[17] This is essentially a subcortical parietal lobe undercutting operation.

Topectomy.—Topectomy[2,3] or topical ablation of a block of cortex from each frontal lobe is a most satisfactory procedure in my opinion. Both the location and the extent of the operation (Fig. 1) can be judged accurately because the entire procedure is carried out under direct vision. An added advantage is the fact that the degree of any cerebral atrophy or arteriosclerosis can be more accurately judged, factors that may influence the amount of the cortical ablation. Finally, any bleeding points can be effectively dealt with so as to make the risk of postoperative hemorrhage virtually negligible. The scalp incision is placed well back of the frontal hairline so that there is no visible evidence of an operative procedure once the hair has regrown.

Although the topectomy operation requires three to four hours because it necessitates a bifrontal craniotomy flap followed by meticulous hemostasis and wound closure, patients usually sit up the day after operation and are out of bed by the second or third postoperative day.

Temporal Lobectomy.—The removal of pathologic or abnormally functioning portions of the temporal lobe frequently relieves psychomotor states characterized by emotional and automatic behavior disturbances (which may or may not be associated with convulsive seizures) related to anterior temporal lobe dysrhythmia.[18,19] The medial, interior, or anterior portions of the temporal lobe

are generally affected in this syndrome and may be easily resected on either side (Fig. 1) without producing neurologic deficits.[18-20]

Stereotaxic Procedures.—Stereotaxic lesions are now being made by Spiegel and Wycis[21] and others to interrupt at the thalamic level the same thalamofrontal circuits that are interrupted in the frontal lobes by lobotomy or topectomy. This is accomplished by placing needlelike electrodes in the dorsomedian (DM) nuclei of the thalamus (Fig. 1) by a stereotaxic apparatus and then passing a coagulating current through the electrodes.

Another stereotaxic procedure developed by Heath and his associates[22] involves the placement of electrodes deep in the posterior medial portion of the frontal lobes in the so-called septal area anterior to the hypothalamus (Fig. 1). Stimulating currents of 4 Ma. or more have been passed through these electrodes with consequent alleviation of pain in cancer patients and improvement of some psychotic states. Whether this effect is solely due to the stimulation of frontohypothalamic fibers or to the small lesions created in this area by the procedure, or both, is under investigation by a number of workers, including Delgado, [23a] Hamlin and his associates[24] and Pool and Clark.[23] The procedure has proved safe, does not cause convulsions, discomfort, or unconsciousness, and often proves surprisingly beneficial in the relief of intractable pain.

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Stereotaxic and ultrasonic procedures show promise of useful application for certain conditions, but are still too new and too complex for ordinary use or for final comment at this time. The use of radioactive seeds for lobotomy is likewise extremely promising and may well supplant all other methods. However, it is possible that malignant changes in the brain may be induced by radioactive substances, so that this technique should be used with caution for the time being.

In summary then, the closed bilateral lobotomy under local anesthesia seems best suited for relief of pain and anxiety in debilitated patients with carcinomatosis, and may be used for the relief of psychotic, "pseudoneurotic," or depressed suicidal states for whom a more radical procedure is not initially indicated. Much the same criteria apply to transorbital lobotomies, which have the lowest incidence of postoperative seizures. Open lobotomies are apt to be safer and more effective than the closed type, but may lead to a higher incidence of postoperative seizures. Topectomy provides excellent visualization of the brain and has proved as effective as lobotomy in over-all results of postoperative improvement, with a lower seizure incidence than in some lobotomy series. Altogether, the final selection of any of these procedures must rest with the individual requirements of the particular patient and should represent the choice of the psychiatrist as well as the neurosurgeon.

INDICATIONS AND RESULTS

Psychosurgery is indicated for the following conditions when psychotherapy, drug therapy, electroshock therapy, and psychoanalysis have failed: schizophrenia; obsessive-compulsive neurosis; manic-depressive psychosis; depressed states (agitated, reactive, involutional); and "pseudoneurotic" schizophrenia.[25]

Ulcerative colitis has also been successfully relieved by topectomy and lobotomy in some patients in whom the intestinal pathology had not become too far advanced. One of my cases has been completely free of symptoms and signs of colitis during the seven years since topectomy; Scoville[6] has reported two cases successfully treated by orbital undercutting and Rix, Lisle, and Levy[26] have had three good results among five patients following bimedial lobotomy. Others, however, have apparently not noted good results following lobotomy for relief of ulcerative colitis.

Pain and anxiety due to cancer may be relieved by lobotomy, orbital undercutting, or by subfrontal electrode implantation.

The phantom limb syndrome may be relieved by parietal lobotomy,[17] which is sometimes preferable to prefrontal lobotomy in these cases.

Drug addiction of certain types can also sometimes be relieved by lobotomy or topectomy.

With regard to the advanced schizophrenic psychoses, the paranoid type with at least some degree of insight into the fact that he is ill and some manifestation of a desire to get well usually fares the best after psychosurgery. The more severe catatonic, hebephrenic, or deteriorated schizophrenic patients usually do not fare as well, but their institutional management may be rendered more satisfactory by psychosurgery. The over-all postoperative results for schizophrenia following any of these procedures is roughly as follows: 33 per cent are effectively improved; 33 per cent are improved to some extent; while 33 per cent show no change.

Obsessive-compulsive neuroses or "pseudoneurotic" schizophrenics,[25] on the other hand, respond best of all to psychosurgery with an improvement rating of 80 to 85 per cent for both these groups. Manic-depressive psychoses do not usually respond nearly as well, although those patients with a predominance of depression are more apt to be improved. Severe depressed states of other kinds such as involutional melancholia and agitated do reactive depressions almost invariably do well after psychosurgery, as or chronic anxiety states, so that at least 85 per cent of such cases have maintained their postoperative improvement during the five to ten or more years they have been observed.

SUMMARY

1. A brief survey is presented describing frontal lobe and other operative procedures (psychosurgery) used for the treatment of disorders of the affect, intractable pain and certain other conditions such as ulcerative colitis, drug addiction, and the phantom limb syndrome.

2. These procedures are discussed in the light of their advantages, disadvantages, and applicability.

3. Thanks to recent developments in this type of brain surgery, serious complications are no longer prevalent, so that many patients are able to lead normal lives with regard to their social, family, and business obligations. Expressed roughly in percentages, it has been found following lobotomy or topectomy over an observation period of two to five or more years, that significant

improvement in terms not only of the underlying psychosis but also with regard to the emotional status, social rehabilitation, work capacity, and earning capacity has been maintained in about 33 per cent of patients with overt schizophrenia and in 80 to 85 per cent of patients with depressions of various types, obsessive-compulsive neuroses or "pseudoneurotic" schizophrenia.*

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*"Pseudoneurotic" schizophrenia is a form of schizophrenia without gross psychotic symptoms like hallucinations, delusions, etc. In this form of schizophrenia the patient shows many neurotic mechanisms which often overshadow or obscure the underlying basic schizophrenic disorder.

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GENETIC FACTORS IN THE DISEASES OF LATER LIFE*

FREDERIC D. ZEMAN, M.D.

NEW YORK, N. Y.

From the Medical Services, The Home for Aged and Infirm Hebrews, and The Mount Sinai Hospital

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THE increasingly effective clarification of medical problems in young people through the application of the principles of genetics leads naturally to the study of hereditary influences in the later years of life. Such an investigation is stimulated by the tremendous increase in the number of men and women reaching the higher age brackets, and by the necessary concern of the practicing physician for understanding the clinical variations of disease in the elderly. The occurrence of hereditary disease in old age has long been known, but relatively little attention has been paid to the interaction of genetic traits and the aging process, or to the changes produced in the body by long-lasting genetic disorders.

Although the science of genetics had its inception as recently as the year 1900 with the rediscovery of Mendel's papers, and modern viewpoints in human genetics are even younger, a concise exposition of its observational and experimental methods and its far-reaching results is impossible short of many volumes.[1] This discussion may be expedited, however, by briefly enumerating certain generalizations that bear directly on our special problem. Since hereditary and environmental influences are today regarded as constantly interacting, their relative importance is recognized in the realization that an organism can respond to external forces only within the limits of its inherited powers. Rarely does the physician see conditions which can be arbitrarily attributed to either heredity or environment alone. Furthermore, hereditary disorders are no longer equated with congenital conditions, since we are continually enlarging our knowledge of malformations evident at birth which have been produced by agents acting upon the fetus in the first few weeks of its life, such as infectious diseases, malnutrition, and anoxia. Many hereditary disorders are functional rather than structural in nature, and are detected only by chemical methods.

The clinician must give up the long-held idea that genetic disorders are either curiosities or rigidly fixed entities. The concept that gene-determined maladies form part of a dynamic process of interaction beginning at the time of conception and in certain cases manifesting themselves throughout life in more or less obvious fashion is the basic theme of this communication, and

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from time to time will be re-emphasized, in accordance with the views of Sorsby and other geneticists. At this point one example will suffice. Families have been studied in which achlorhydria may be demonstrated early in life. Of these persons, certain ones develop pernicious anemia. In those so afflicted, gastric carcinoma develops in a far higher percentage than in the general population. The mere statement of this clinical sequence highlights our lack of knowledge of the factors determining the progression from one stage to the next, but at the same time vividly illustrates the dependence of the terminal state on the genetic abnormality.

The observation that hereditary structural or functional abnormalities may be present without any clinical manifestations has been developed by Neel[2] into the concept of the "genetic carrier." In his comprehensive listing of these silent genetic traits, we find such common conditions of later life as hyperuricemia, the precursor of gout, hyperglycemia predisposing to diabetes, and personality disorders leading to psychiatric conditions. Among the rarer genetic clinical states he listed sicklemia and sickle-cell anemia, spherocytosis and hereditary hemolytic icterus, hypercholesterolemia, and xanthomatous deposits in the skin and arteries. By going one step further and studying the sequelae of these disorders we are able to enumerate many steps in common clinical sequence, which throw light on over-all problems of pathogenesis. The detection of genetic carriers by means of special tests offers the possibility of early diagnosis and possible preventive measures, as well as broadening our knowledge of human genetics. Such studies have been carried out on the relatives of patients suffering from gout by Stecher, Hersh, and Solomon[3] and by Smyth, Cotterman, and Freyberg.[4]

From the practitioners' viewpoint, Sorby's warning as to the doubtful specificity of clinical appearances is particularly significant. He pointed out that "the appearances of an affection definitely of genetic or definitely of environmental origin may be clinically indistinguishable."[5] The diagnostic decision can be arrived at only by careful study of the patient's whole history. Furthermore genetic syndromes may present themselves in incomplete form. Only within recent years has it been established that pulmonary arteriovenous aneurysms, which are being diagnosed with increasing frequency, are part of the condition long known as familial hereditary telangiectasia.[6] The typical skin lesions of this condition are often obvious, but in some cases may be found only after careful search in the presence of frank arteriovenous shunts in the lungs. The basic abnormality may therefore be present in mild form and its significance overlooked in the presence of a dramatic secondary manifestation.

Before considering the interaction of genetic traits and the aging process, we must consider longevity itself as an inherited characteristic. Pearl[7] and many others established by analysis of family histories that long-lived individuals have a preponderance of long-lived ancestors. On the other hand, Dublin and his co-workers[8] emphasized that the startling increase in life expectancy of the past fifty years is to be attributed to environmental conditions such as improvements in public health, pure food and water, as well as improved methods of medical care. The obvious fact that we can improve environmental con-

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ditions but can hardly have any influence on the inheritance of longevity lies outside the scope of our present thinking. More clearly related to our theme, however, is Kallman's study of senescence in twins. "Whereas fraternal twins who have lived in the same environment often have different courses in senescence, identical twins raised in different environments often have the same types of disorders and pathologic conditions quite consistently at the same time of life and in the same manner."[9] These findings make clear the far-reaching effects of genetic characteristics, and must influence our attitudes toward common clinical problems where the conditions of such an ideally controlled experiment are rarely to be satisfied.

In considering the effect of a long life on genetic characteristics, we can clarify our thinking by dividing environmental influences into external and internal categories. The external influences are self-evident. By internal influences we refer primarily to the aging process itself, in the sense of a variation in Bernard's *milieu interne*, although the effects of associated diseases must also be included here. Under the aging process we include all those conditions occurring with age which cannot be attributed to known disease processes, such as cellular dehydration, changes in hydrogen-ion concentration, in calcium content, in cell permeability, and variations in homeostatic response to local environmental changes. Studies yet to be made may well involve such intra- and extracellular changes as the explanation of the observation that individuals bearing the gene for diabetes or for gout may go through life symptom-free, and in the absence of any obvious cause finally develop the disease in the fifth, sixth, or seventh decade of life. Longevity therefore gives more opportunity for genetic traits to be influenced by internal and external environmental changes, and affords more opportunity for latent disorders to become manifest. Pseudolatency must also be recognized in that the signs of a genetic disorder may be present in diagnosable form but are undetected either through oversight or lack of knowledge. Such latent conditions may escape observation because of overshadowing complications, as in the case of pulmonary arteriovenous aneurysms, which at times may become the site of a subacute bacterial endarteritis, presenting at first examination the alarming symptoms of bacterial invasion of the blood stream.[10]

In considering the specific genetic disorders from the standpoint of the carrier state, the primary clinical manifestations, and the secondary sequelae, space will permit only some comments on the principal conditions. Briefer mention will be given, however, to some of the rarer conditions because these unusual states often throw light on simple mechanisms that in turn clarify more complicated reactions. Since this study is primarily concerned with these conditions in later life, specific allusion will be made to reported and personal cases of advanced age whenever possible, but examples from the periods of early and late middle age will also be utilized in order to clarify general principles, and in the hope of stimulating the search for important hereditary disorders that now may be overlooked in the aged. While the effort is made to trace the relationship between the specific disorder and its late clinical sequelae, the physician must bear in mind that these patients may eventually succumb to diseases

with no evident relation to the hereditary disorder. A 69-year-old man who had been known to have Gaucher's disease for seven years was recently admitted to The Mount Sinai Hospital suffering from arteriosclerotic heart disease, anginal syndrome, auricular fibrillation, and congestive failure. The symptoms of cardiac insufficiency responded promptly to the usual treatment. This patient's brother, who also suffered from Gaucher's disease, died at the age of 65 years as the result of multiple carcinomas of the sigmoid due to multiple adenomatous polypi of the large intestine.

DISORDERS OF METABOLISM

Among the hereditary disorders of metabolism, Garrod's "inborn errors," we note that pentosuria and renal glycosuria may persist throughout life without harmful effects and without symptoms, unless an examining physician mistakes the urinary-reducing substances for those of true diabetes. Cystinuria in adults may be symptomless until a renal calculus forms and causes colic. Garrod[11] cited the case, reported in 1870 by Sir Henry Thompson, of a man 81 years old for whom the surgeon crushed a cystine bladder stone and who had passed a similar stone thirty-nine years before.

Alkaptonuria, in spite of the enzyme deficiency that prevents the breakdown of homogentisic acid, is a relatively harmless hereditary condition which is compatible with long life in spite of the discoloration of cartilages and other tissues known as ochronosis. In a recent study Galdston, Steele, and Dobriner[12] reported three cases, a man of 65 years, a man of 60 years, and a woman of 94 years. All these patients showed the characteristic changes of the disease as well as the usual sequelae of osteoarthritis and calcification of the intervertebral discs. Alkaptonuria is an end-stage interruption of the phenylalanine-tyrosine metabolism, an intricate series of chemical changes well illustrated in diagrammatic form in Sorsby's book and in Harris' monograph.[13] Another familial condition resulting from disturbance of these chemical reactions is albinism, which is due to a defect in melanin pigment production, a condition that persists into later life with relatively few symptoms.

The influence of heredity in both diabetes and gout has been known and studied for many years with the result that we are now able to detect genetic carriers and to counsel diagnostic and preventive measures in the relatives of patients whose families show a high incidence of these diseases. Smyth, Cotterman, and Freyberg[4] have shown that only one-tenth of patients with genetic hyperuricemia ever develop clinical gout. The serious sequelae of these diseases need no elaboration, although the high incidence of arteriosclerosis in both these maladies may be due to an associated hereditary disturbance of cholesterol metabolism, as suggested by Adlersberg.[14] More difficult to explain is the appearance of these conditions for the first time in middle life or beyond. About 45 per cent of all cases of diabetes develop after 50 years of age. While the average age of onset in gout is 40 years, it may manifest itself for the first time as late as the eighth decade. What influences determine the transition from the genetic carrier state to frank clinical manifestations are not now known, but obesity, infections, endocrine imbalance, and emotional stress are important

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predisposing factors in diabetes. The chronicity of both these diseases explains why death in the majority of cases occurs at advanced ages. According to Joslin's[15] series, death from diabetes occurs in 31.1 per cent of men between 60 and 69 years, in 31 per cent between 70 and 79 years, and in 16.2 per cent at 80 or beyond. The mortality figures for women are only slightly lower.

Among the hereditary lipidoses we have already singled out Gaucher's disease, characterized by the storage of kerasin throughout the body, because it is encountered in patients of advanced age. Among its late sequelae we may enumerate hypersplenism and hypertension as well as lesions of the brain and the bones. Of far greater importance is familial hypercholesterolemia, also known as primary cholesterol lipidosis, because of its relationship to atherosclerosis in general and to coronary artery disease in particular. Boas, Parets and Adlersberg[16] found elevated serum cholesterol in seventy-one individuals, or 58 per cent, of a group of 122 patients with proved coronary atherosclerosis whose disease began under the age of 50 years. Hypercholesterolemia was found in all or most of the siblings of one-third of fifty families of patients with atherosclerosis. Wilkinson and his group[17] have reported on the mode of inheritance based on the study of several large kindreds. Adlersberg, Boas, and Parets[18] postulate that familial xanthomatosis, the severest form of the disease, often associated with coronary sclerosis, develops in the carriers of two abnormal genes (homozygotes), while the milder form is manifested in uncomplicated coronary sclerosis in persons under 50 years who are the bearers of only one abnormal gene (heterozygotes). Extension of their studies by Boas and Adlersberg[18a] to a group of patients with coronary artery sclerosis developing after 60 years of age suggested that the derangement of lipid metabolism in these cases is a more indolent one than in the younger patients. The incidence of hypercholesterolemia in the sibs of the older group was as high as in the younger group.

CARDIOVASCULAR SYSTEM

While hypercholesterolemia is a familial metabolic disorder affecting the cardiovascular system as well as other tissues of the body, we must also consider the hereditary structural defects of the heart and blood vessels. Congenital heart disease has been rarely reported in families,[19] and must be mentioned because certain types of cardiac malformation are well known to be compatible with advanced age. More significant are the recent studies on arachnodactyly or spider fingers, seen clinically in young people and commonly associated with eye defects and heart lesions, often terminating in heart failure or aortic rupture with dissection.[20] Recent studies have emphasized as the basic cause of the aortic involvement the occurrence of cystic medial necrosis, first described by Erdheim[21] as a cause of dissecting aneurysm in middle-aged and elderly people with hypertension. Aneurysm in association with arachnodactyly has been described in a patient 52 years of age.[22] Goyette and Palmer[20] pointed out that "cystic medionecrosis is the basis of nearly all dissecting aneurysms regardless of age," and that these changes may occur as isolated lesions in families

with arachnodactyly, or a *forme fruste* of this hereditary syndrome. Alert observation of older individuals may disclose other clinical signs in patients with aortic dissection and rupture who heretofore have been dismissed with the facile diagnosis of aortic arteriosclerosis. McKusick's[23] work with rats suggests the additional possibility of an experimental approach.

Essential hypertension is a common disorder beginning in middle life and running a benign course for twenty to thirty years. Clinicians have long recognized its familial occurrence. In a recent symposium aimed at clarifying some of the basic problems of this disease, Evelyn[24] stated, "My own investigations have led me to accept heredity as the most important etiologic factor, if not indeed, the only one which has been demonstrated with a satisfactory degree of statistical validity—age, sex, race, diet, obesity and psychogenic factors notwithstanding." Ayman,[25] at the same meeting, quoted his own studies on 1,524 members of 277 families and postulated that "the hypertensive is born with a transmitted high-strung personality and hyperactive sympathetic arteriolar system." Evaluation of the genetic factor in this important disease depends on the further longitudinal study of large numbers of families and the collection of blood pressure figures in twins at various stages of life.

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That hemorrhagic familial telangiectasia had been known so long before its association with pulmonary arteriovenous aneurysms was noted, gives some idea of the important clinical and pathologic relations that remain to be disclosed in genetic disorders. The vascular lesions characteristic of this condition affect the skin, the mucous membranes of the nose and throat as well as of the gastrointestinal tract, rarely of the meninges. They increase in number with advancing years, become more and more liable to bleeding, and lead to severe anemia as the result of recurrent epistaxis, hemoptysis, and hemorrhage from the stomach and intestines. One woman of 60 years has been known to have this disease for twenty years and has been admitted to the Mount Sinai Hospital twenty times for blood replacement therapy. Over the years she has developed a gradually increasing hepatosplenomegaly, and mild congestive heart failure ascribed to the constantly aggravated anemia. In older patients with recurrent bleeding from the lungs, stomach, or intestines, search for the typical telangiectatic areas in the skin and mucous membranes will at times disclose them in small number but enough to establish the diagnosis and explain the symptoms, when all other tests fail.

CYSTIC DISEASE OF THE KIDNEYS

Polycystic kidneys have high points of familial incidence in the very young and in the middle years. In the latter group the condition is characterized by gradual increase in the size of the cysts and by steadily decreasing functional capacity of the kidneys leading to hypertension, cardiac enlargement, cardiac failure, uremia, or cerebral hemorrhage. Recently Bigelow[26] and Poutasse, Gardner, and McCormack[27] have added aneurysms of the "berry" or congenital type affecting the circle of Willis to the lesions associated with polycystic kidneys. Cystic lesions also occur in the liver and pancreas. Highly complicated combi-

nations of congenital and acquired lesions may be encountered, as in a man of 73 years who sought treatment for arteriosclerosis obliterans with recurrent ulcers of the feet. In the hospital a left-sided abdominal tumor was found, the nature of which was under investigation, when he developed pyelonephritis with bacteriemia. *Pseudomonas aeruginosa* was recovered by blood culture. At post mortem was revealed a solitary infected polycystic left kidney with agenesis of the right kidney, of the right ureter, and of the seminal vesicle. In addition were found multiple cysts of the liver, chronic bleeding peptic ulcer, chronic cholecystitis and cholelithiasis, bilateral cervical ribs, and polyps of the cecum and the transverse colon. In Bigelow's patients, aged, 33, 62, and 52 years at death, a similar variety of anomalies led to the suggestion that polycystic renal disease may be one phase of a disseminated congenital disorder analogous to tuberous sclerosis, neurofibromatosis, or Lindau-von Hippel's disease (hemangioma of the cerebellum and retina).

DISEASES OF THE BLOOD

The relationship of pernicious anemia to the precursor state of achlorhydria and the sequel, gastric carcinoma, has already been mentioned. This knowledge serves to alert the clinician to the study of the patient's relatives in order to make an early diagnosis, and to have frequent x-ray examinations of the stomach of patients in whom the diagnosis has been established.

Familial hemolytic anemia, characterized by spherocytosis and increased red cell fragility, is a relatively mild disorder of long duration, characterized by hemolytic crises resulting in fever, jaundice, abdominal pain, and anemia. The genetic abnormality resulting in spherocytosis is considered to be the basis of this disorder. Not long ago a woman of 70 years was admitted to The Mount Sinai Hospital with a history of gastrointestinal disorders for many years, on whom the diagnosis was made for the first time without difficulty on the basis of typical findings. Of particular interest was the family history. A brother who died an accidental death had always been jaundiced. One of the patient's sisters had had a cholecystectomy and one niece had had both a splenectomy and a cholecystectomy. Gall stones are a common complication of the condition, and in younger persons may lead to suspicion of the underlying disorder.

Sickle-cell anemia develops in Negroes who have inherited the sickle-cell trait, which is transmitted as a Mendelian dominant. The disease, which occurs in only a few of the individuals showing sickling of their red cells, usually begins in childhood and is generally not considered compatible with long life. Fetter and Schnabel[28] have reported sickle-cell anemia in patients over 45 years of age, describing a man of 62 years and a woman of 47 years. They quoted Sydenstricker's[29] three cases in patients of 78, 72, and 62 years, as well as the observations of Steinberg[30] and Kracke[31] on the occurrence in older patients. Evidently the incidence is high enough to make the search obligatory in the anemias of elderly Negroes. The disease may apparently have its onset in young adult life, and after repeated attacks the disease may disappear, or it may have its onset in middle life, running a mild course.

Thalassemia is due to an inherited defect in erythrocyte formation and is differentiated into major and minor forms, differing greatly in mode of onset and in severity. Valentine and Neel[32] studied thirty-four members of four families and proposed the hypothesis that inheritance of the defect from both parents (homozygosity) resulted in the full-blown disease (thalassemia major), and inheritance from only one parent (heterozygosity) resulted in the less severe form (thalassemia minor). In this type there is only slight impairment of health and no effect on longevity.

ALLERGIC DISORDERS

The hereditary nature of asthma has been observed by clinicians for over 250 years, but the exact manner of genetic transmission and its relationship to hay fever, eczema, and urticaria have been the source of great confusion and argument among students of these diseases. Coca's concept of atopy or atopic diseases is, however, based on the peculiar features of certain allergic disorders which all have a hereditary basis. The recent clinical and genetic study of bronchial asthma by Schwartz[33] is based on 191 asthma patients and fifty patients with baker's asthma. He shows that asthma is an inherited disease and that a genetic relationship exists between asthma, vasomotor rhinitis, Besnier's prurigo, and hay fever. Eczema, migraine, psoriasis, gastrointestinal allergy, ichthyosis, and epilepsy are genetically unrelated to asthma.

Asthma and its related atopic disorders may appear for the first time in middle life or even in old age. My colleague, Dr. Selian Hebald, once treated a woman of 82 years in her first attack of typical allergic asthma. At times these disorders beginning in early life seem to become modified and assume less severity with advancing years. Bronchial asthma of long standing may be the cause in old age of nasal polyps, emphysema, bronchitis, recurrent bronchopneumonia, and interstitial pulmonary fibrosis with eventual right heart failure due to so-called cor pulmonale.

MUSCULOSKELETAL DISORDERS

Among the long-standing disorders of the bones and joints which have been shown to be genetically determined are multiple cartilaginous exostoses and achondroplasia. This latter condition is compatible with long life, as shown by a remarkable woman of 65 years with this condition, who has been under our care for the past three years at The Home for Aged and Infirm Hebrews. Paget's disease, osteitis deformans, has been considered of hereditary origin by many authors. Hirsch[34] has recently reviewed the subject and considers that the figures on familial occurrence are more than accidental, and that the possibility is strong that osseous changes occur in a genotypic milieu. Of extreme significance is the late occurrence of this disease and the fact that about 3 to 5 per cent of patients develop bone sarcoma.

Stecher and his co-workers[35] have studied the heredity of Heberden's nodes, commonly encountered in older women. Their findings confirm that this disorder is inherited as an autosomal sex-influenced trait, dominant in women and

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recessive in men. Of importance to this presentation is their statement that "penetrance is not complete until an advanced age. The incidence of idiopathic Heberden's nodes found by examination of 2,200 white women varied from 0.4 per cent in the fourth decade to 30 per cent in the ninth."

The study of the genetics of rheumatoid arthritis by Stecher's[36] group yielded data that required careful interpretation. The authors pointed out that heredity is an important factor in this disease, but that "the data are extremely irregular due in part to irregular penetrance and a number of exogenous influences which affect expressivity."* These studies illustrate some of the difficulties inherent in problems of human genetics, and at the same time emphasize the utility of the methods and viewpoints in elucidating chronic diseases.

Stecher and his co-workers[37] had previously studied heredity in ankylosing spondylitis on the basis of fifty families. The important role played by heredity was shown by the numerous reported cases of multiple involvement in sibships and in at least three pairs of concordant identical twins. Their data indicate that ankylosing spondylitis is due to an autosomal dominant factor with 70 per cent clinical expression in males and 10 per cent in females.

Among the hereditary muscular disorders which we include within our field of interest are the facioscapulohumeral type of progressive muscular dystrophy, myotonia congenita (Thomsen), paramyotonia congenita, myotonia dystrophica (Steinert), and peroneal muscular atrophy (Charcot-Marie-Tooth). Tyler and Stephens[38] have described the clinical manifestations and inheritance in a large family afflicted with facioscapulohumeral muscular dystrophy. The onset of symptoms or signs recognizable either by the patient or his family usually occurred between the ages of 7 and 20 years. Most common age at onset, judged by symptoms, was 13 to 15 years. A number of individuals were unaware that they had inherited the disorder. One elderly woman first knew of her disability at the age of 55 years, when it was pointed out to her by the physician who noted the disease in her children. Patients with this disorder, while handicapped, ordinarily suffer no limitation of life expectancy.

Likewise in the rare diseases, myotonia congenita and paramyotonia congenita, there is no appreciable effect on the lifespan.[39] Myotonia dystrophica may have its onset in middle or later life, and is noteworthy because of associated cutaneous, ocular, and endocrine changes which are referred to in the discussion of hereditary skin disorders.[42] Peroneal muscular atrophy has been widely studied in Europe and the United States. While the onset is in adolescence, the progress may be slow. In affected areas, such as North Carolina, many minimally affected cases are found. This necessitates careful study in order to establish hereditary interrelationships.

CUTANEOUS DISORDERS

The numerous hereditary disorders of the skin and its appendages are comprehensively treated in Cockayne's[40] classic volume. Of those persisting into later life we may mention ichthyosis vulgaris, anhidrotic ectodermal dysplasia, keratosis follicularis, pityriasis rubra pilaris, pseudoxanthoma elasticum, benign

*"Penetrance" means involvement; "expressivity" refers to clinical manifestation.

familial pemphigus, xeroderma pigmentosum, and neurofibromatosis. The last two are particularly striking because in xeroderma, basal-cell carcinoma is a frequent complication, and in von Recklinghausen's disease sarcomatous metaplasia occurs in 15 per cent of the cases. In general, skin disorders behave as do other hereditary conditions as regards longevity, namely, the milder cases are to be found in the higher age groups. This would be true for example in ectodermal dysplasia, where diffuse and severe involvement always shortens life.

Many hereditary disorders of the skin are associated with other lesions in various parts of the body. The Peutz-Jeghers syndrome is a familial disorder characterized by intestinal polyposis in association with melanotic spots on the lips, oral mucosa, and digits.[41] Touraine[42] has grouped together all the hereditary cutaneous atrophies characterized by premature senescence, including among others, Gilford's progeria, emphasizing the associated cataracts, endocrinopathies, and disorders of mental and somatic development. He classified these disorders according to time of onset into precocious and late or adult types, and laid stress on the multiplicity of clinical forms, some incomplete, some more extensive, representing transitions between the varied but related clinical pictures.

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NEUROLOGICAL DISORDERS

Among the hereditary disorders of the central nervous system which may persist into later years, we note the hepatolenticular degeneration of Wilson, familial periodic paralysis, familial tremor, and paralysis agitans. Regarding this last named condition, the work of Mjönes, quoted by Pratt,[43] lends weight to the belief that hereditary vulnerability of the extrapypramidal system may determine the development of Parkinson syndrome as a result of either cerebral arteriosclerosis or encephalitis. The clinical range of Wilson's disease has been broadened by Uzman and Denny-Brown,[44] who have identified the pseudoscleroses of Westphal, Strümpell, and Fleischer as milder, more chronic forms of the disease, identifiable by the "wingflapping" tremor and the Kayser-Fleischer corneal ring. These cases may occur later in life and run a more prolonged course.

In Talbott's[45] description of periodic paralysis, he pointed out that the symptoms usually develop in the first or second decade of life, and are most troublesome at puberty or during adolescence. There is a tendency for the attacks to diminish in frequency and in intensity during middle life and to disappear in late adult life. He cited Goldflam,[46] however, who observed five patients, 50 years or older, who continued to be troubled by periodic attacks. Two died, at 54 years and 60 years, without having enjoyed any respite from attacks since youth.

Familial tremor, often miscalled "senile tremor," is important for the clinician because patients fear that it indicates the onset of Parkinson's syndrome.[47] Occasionally a family history may be elicited, but the absence of the signs of other tremor-producing diseases makes reassurance easy. I have recently noted the gradual development of head shaking, during the fifties, in

a woman whose mother had had an identical condition which also began in middle life.

MENTAL DISORDERS

In the chapter on genetics and psychiatry contributed by Slater[48] to Sorsby's textbook, we find an excellent study of the development of our present-day attitudes. This is an active area of conflict among the various schools of psychiatric thought because of the supposed implication for theories of pathogenesis. Kallman's[49] classic volume, *Heredity in Health and Mental Disorders*, is devoted principally to the results of his life-long study of twin-pairs, and gives particular attention to senescence and the mental disorders of later life. He has emphasized that "similarities in the intellectual performances, adaptive potentialities and adjustive patterns of senescent one-egg twins generally exceed that seen in two-egg pairs. The manner in which genetically determined variations in aging and longevity compare with those in intellectual and adaptational abilities is conclusive evidence of the considerable extent to which genic elements influence a persons's variable capacity for maintaining a state of physical and mental health throughout life."[50]

Hereditary effects in older individuals can best be considered in relation to time of onset, and for this reason we may set up two large groups: the mental disorders originating in early life and persisting into late maturity, and those which become manifest for the first time in old age. The first category includes psychoneuroses, manic depressive psychosis, schizophrenia, and Huntington's chorea, while in the second we find the chronic brain syndrome with its varied associations, including the group formerly designated as senile dementia.

Increasing attention to the mental difficulties and disordered behavior in older patients has led Goldfarb[51] and other psychiatrists to emphasize the persistence of psychoneuroses from earliest childhood to old age. In the later years these symptoms may be confused with the manifestations of organic brain disease and lead to erroneous attitudes on the part of physicians and nurses. The complex character of psychoneuroses and the indefinite outlines of diagnostic groupings have made statistical studies difficult and dissuaded many clinicians from consideration of a possible genetic background. This whole subject has been ably analyzed in a recent study by Haskell,[52] who has traced the manifestations of psychoneurosis through five generations of a large Anglo-American Jewish family. Predisposition to neurotic symptoms was inherited as an autosomal dominant in this family. One observation of the author has a practical bearing. "By recognizing the familial tendency of the condition, it should be possible for the physician to warn a family with the trait, to ease environmental stresses likely to produce a neurotic state in an otherwise normal person." Clinicians are today becoming more aware of the psychoneurotic influences in the complex symptoms presented by their elderly patients, and in time should achieve therapeutic insight as well as diagnostic accuracy.

To evaluate varied viewpoints as to the genetic basis of schizophrenia would be out of place in this paper. So much emphasis has been placed on environmental factors that it is important for the internist to realize that Kallman,[49]

Böök,[53] and other students of heredity believe strongly in the importance of genetic influences in this disease. The frequency of elderly schizophrenics in mental institutions and their occasional appearance in the consulting room and the general hospital indicate that the lifespan may not be appreciably affected.

Manic depressive psychosis usually begins in adolescence or early adult life and is commonly noted to be familial in occurrence. Kallman's twin studies indicate not only a gene-controlled tendency to excessive mood swings but also a tendency to obesity, pointing to an associated neurohormonal disturbance. The persistence of this disorder into old age is well illustrated by Guttmacher's[54] *America's Last King*, a psychiatric study of King George III. This monarch suffered his first attack at the age of 26 years. The fifth and fatal episode occurred at 84 years. This exemplifies the persistence of a genetically determined psychosis recurrent throughout a long life. Much of the confusion in earlier studies of the hereditary background of mental disorder has been due to diagnostic overlapping, with the result that schizophrenia, manic depressive disease, reactive depression, and involutional disorders have been lumped together. More precise differentiation yields a clearer picture of the inheritance of certain of these disorders. Realization that they are not confined to younger age groups increases diagnostic awareness.

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One of the first neuropsychiatric disorders to be established definitely on an hereditary basis was Huntington's chorea, first described in 1872, and traced back 300 years in an unbroken line. The disease may begin at any age but commonly takes its onset in the fourth decade. It is characterized by coarse choreiform movements, increasing in severity, and a progressive dementia. The average duration is ten to fifteen years, but great variations have been reported in all its clinical features, including one patient whose chorea began at 50 years and who lived to 75 years with well-preserved mentality. Wilson[55] emphasized that the differential diagnosis from senile chorea depends on the relatively mild symptoms and on the absence in the latter group of mental deterioration and of a family history.

The stereotype of cerebral arteriosclerosis causing mental disorders in the old has long been questioned, but the exact role of genetic influences in the development of the chronic brain syndrome associated with psychoses is yet to be determined. For the presenile group, Pick's, Alzheimer's, and Jakob's disease, the evidence favoring genetic control is suggestive but not conclusive. For the entire group of old age mental deterioration the evidence is less clear, even though Kallman found that in some of his one-egg twins both members developed senile psychoses at the same time in spite of differences in environment and in social status. He summed up his findings thus: ". . . the etiology of the various forms of a senile psychosis is based on an interplay of complex determining factors, such as age-susceptible personality traits, reduced adaptive plasticity, and those gene-specific phenomena controlling growth and decline."[49] Realization of the variability of the clinical pictures and of the importance of careful consideration of the whole life history in connection with painstaking clinical observation will bring fresh and stimulating insights into these difficult problems.

THE SPECIAL SENSE ORGANS

A few notes will serve to bring into the orbit of our discussion the important genetic disorders of the eyes and ears that play significant roles in the later years of life. Sorby's[56] monograph, *Genetics in Ophthalmology*, is a rich source of information. In the introduction he pointed out that, with the control of infectious diseases, particularly of ophthalmia neonatorum, there has been a complete change both in the age incidence and in the causes of blindness. Elsewhere he stated that "nearly 80 per cent of those registered as blind in England and Wales are over the age of 50 years, and the leading causes of blindness are cataract, glaucoma, and the senile degeneration of the fundus. Each of these affections may well have more than one cause, and there is at least strong presumptive evidence that hereditary tendencies play a not inconsiderable part."[57] In Norway, Holst has found that one-half of the cases of blindness are due to genetic factors.[58] Other ocular disorders seen in old people which have a genetic basis are myopia, with or without night blindness, retinitis pigmentosa, general fundus dystrophy, which stimulates conditions of environmental origin, and cysts of the macula. Many of the genetic abnormalities of the eyes are found in association with abnormalities of other parts of the body, as in arachnodactyly and in the Lawrence-Moon-Biedl syndrome.

As regards the hereditary disorders of the ears, we find that "otosclerosis, the most common cause of impaired hearing in later life, appears to be due in most cases to the action of one or more dominant genes."[59] Some of the difficulties in establishing the inheritance of otosclerosis are discussed by Lindenov,[60] who pointed out that there are probably actually more cases than are diagnosed, as the lesion manifests itself clinically only when the stapes is involved, that is, in only one-third of the cases, and further because in older persons it may be mistaken for nerve deafness. There is, in addition, a form of hereditary labyrinthine deafness, which rarely may be unilateral.

As regards the special sense organs, it is apparent that genetic factors are of extreme importance clinically and will increase in significance in direct relation to the intensity of the study of atypical cases.

RELATION OF LONGEVITY, AGING, AND HEREDITY TO CANCER

The complicated problem of the relation of longevity, aging, and heredity to the development of benign and malignant tumors can only be touched upon briefly in order to round out the picture of genetic factors in the diseases of later life. The foregoing discussion of specific conditions has emphasized the relationship of gastric carcinoma to pernicious anemia and achlorhydria, of bone sarcoma to Paget's disease, of sarcoma to neurofibromatosis, and of basal-cell carcinoma to xeroderma pigmentosum. In some of the persons afflicted by these familial disorders, and end stage is the development of a malignant tumor.

To these conditions we must add familial intestinal polyposis, well studied by Gardner,[61] by Schaffer,[62] and more recently by Donovan.[63] The incidence of carcinoma is extremely high in these cases, and the tumor formation is di-

rectly related to the intestinal polypi. The carcinomas develop unusually early in these cases, often before 35 years of age. When cancer develops as a result of acquired polyposis, a later onset is usually observed. Plenk and Gardner[64] have recently described a family group of sixty-four persons of whom six individuals showed the unusual association of polyposis of the colon and multiple osteomas (leontiasis ossea).

Other tumors which are definitely hereditary are retinoblastoma and cerebral angioma, which are mentioned only for completeness since they occur early in life.

The occurrence of these genetically determined or influenced neoplasms must be considered in connection with the observations of McFarland and Meade[65] and Macklin's[66] work, which indicate that the incidence of similar tumors in both members of identical twins is greater than would be expected on the basis of chance. Studies of the incidence of cancer in the relatives of patients who have died as a result of cancer indicate a heightened occurrence above that in the control cases. The tremendous amount of work on experimental tumors using strains of pure-bred mice gives great weight to the importance of the genetic constitution as modified by many additional factors. Little's[67] excellent review and Macklin's[68] work should be consulted for an extended discussion of these questions. An important point, mentioned by Little, is that some carcinogenic agents may also serve as the producers of mutations, indicating a chemical susceptibility of the chromosomes, and a relationship between these two revolutionary reactions, occurring in the extremes of the lifespan.

Ewing,[69] many years ago, expressed the belief that the only connection between aging and cancer was the lapse of time. He did, however, point out that an important principle governs senile atrophy in all organs, namely, that during the atrophic process surviving epithelial tissue may not only escape atrophy but may exhibit increased powers of growth which tends to assume malignant properties. This is shown in the sudden and excessive growth of single hairs which often appear on the skin of aged persons.

Longevity in itself is of the greatest importance in tumor formation because it provides greater time of exposure to the cumulative interactions of genetic traits and environmental influences. Increased duration of life also serves to involve more members of one family, since in the past some members died before reaching the age of incidence. Much of the statistical work on cancer in relation to age and occurrence is hampered by the limitations of clinical diagnosis, since a certain number of cases will be either diagnosed incorrectly or missed, as Willis'[70] study of post-mortems showed.

These brief considerations indicate a definite genetic basis for a few tumors only, but emphasize that longevity, itself genetically determined in part, serves as the necessary basis for prolonged exposure of the organism to the greatest range of external and internal influences, only a few of which are as yet sharply defined. From a practical point of view, Macklin[68] has suggested that "the knowledge that some forms of cancer are determined by heredity should be a diagnostic tool to be used intelligently by the medical profession." She feels

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that indiscriminately repeated x-ray examinations of the gastrointestinal tract are economically unjustifiable, and presents the alternative of concentrating diagnostic efforts on those persons who have lost a near relative of cancer of the lung, intestines, or rectum.

SUMMARY

In this study the hereditary disorders persisting into later life have been considered as the results of the interaction of genetic traits and the aging process, and particularly with reference to their participation in dynamic disease processes in which late sequelae assume overshadowing importance. The discussion has brought out the wide range of genetically determined pathologic processes encountered in middle age and old age, ranging from such rarities as alkaptonuria, hemorrhagic telangiectasis, Gaucher's disease, and polycystic kidneys, to such commonly encountered entities as diabetes, gout, essential hypertension, allergic reactions, pernicious anemia, psychoneuroses, and psychoses. The interrelationships of heredity, longevity, aging, and neoplasia, both benign and malignant, have been considered briefly. These considerations all serve to emphasize the need for further investigation of these complex problems both in the laboratory and at the bedside. As clinicians we must increase our awareness of genetic influences, and become familiar with genetic theory and method. We must study family histories more intensively and develop means for the detection of genetic carriers. We must be on the alert for the mild, the masked, the modified, and the atypical forms of the more clearly defined syndromes. We must abandon our outmoded attitudes of pessimism and seek accurate early diagnosis upon which effective preventive measures may be based, since some of these conditions are already amenable to specific treatment. Search for these easily overlooked interrelationships lends new fascination and new promise to the study of disease in the aged.

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IS ATHEROSCLEROSIS A CONDITIONED PYRIDOXAL DEFICIENCY?

HENRY A. SCHROEDER, M.D.

ST. LOUIS, MO.

From the Hypertension Division, Department of Internal Medicine, Washington University School of Medicine, and Barnes Hospital, under a grant-in-aid from the National Heart Institute, United States Public Health Service

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DEFICIENCY of vitamin B_6 in monkeys has been shown to produce vascular lesions similar to those found in human atherosclerosis by Rinehart and Greenberg.[1,2] This work has been confirmed.[3] The only other known cardiovascular disease caused by deficiency of B_6 is arterial hypertension in rats.[4,5] Inasmuch as lack of or antagonism to this single coenzyme can cause degenerative vascular disease in animals, it is pertinent at this time to explore the possibility that atherosclerosis in man is due to or initiated by a conditioned deficiency of intermittent nature.

To do so we must examine the intake of B_6* in the diet, consider the actions of the coenzyme in biochemical reactions believed to be important in atherogenesis, discuss ways in which the coenzyme might be partly inactivated, and look at the dietary intake of foods suspected of having a role in atherogenesis, particularly of fats. If pyridoxal is involved, available knowledge suggests that deficiency is confined to only one or at most a few of its many known functions.

The initial lesions in monkeys appear to involve the intima and, to a less extent, the media of arteries. Accumulation of substances resembling mucopolysaccharides was observed, with proliferation of the cellular elements of the intima and formation of collagenous and elastic tissue fibres. Deposition of lipid appeared in later stages of the lesions. There is some evidence that a similar sequence of events occurs in man.[2] Since pyridoxal as a coenzyme is concerned with a variety of fundamental reactions involving amino acids and fats, it is possible that these vascular lesions may be the result of a profound metabolic disturbance in the mucoid interfibrillary ground substance of the intima of vessels.

DIETARY INTAKE OF B_6 IN THE UNITED STATES

A number of analyses of various foods have been made for pyridoxine, pyridoxal, and pyridoxamine. Probably the most accurate analyses are those

*The term "B_6" is used to include pyridoxine, pyridoxamine, and pyridoxal, the members of the B_6 group. The coenzyme is believed to be active as the aldehyde phosphate, and the aldehyde and amine are the forms prevalent in animal tissues.

of Rabinowitz and Snell.[6] Although quite incomplete, they include concentrations of all three forms of the vitamin and show clearly that over 80 per cent of the B_6 in fresh animal tissues was present as pyridoxal and pyridoxamine, the former being the predominant form in all tissues but liver. On the other hand, pyridoxine was the usual form encountered in vegetable material. The most extensive studies were made by Cheldelin and Williams[7] using a yeast growth method, after enzymatic digestion of the food, more or less specific only for pyridoxine. Other methods include autoclaving in order to liberate the vitamin, growth of rats and larvae, and chemical analyses.

Although different analytic methods include or exclude potent forms of the vitamin, a few significant observations are pertinent to any question of dietary intake. About one-half is lost when whole wheat flour is processed.[8] Canned vegetables contain little pyridoxine[9]; fresh vegetables and fruits are fairly good sources.[7] The processing of milk[10] and meat[11] and especially cooking and stewing[11] result in substantial losses of pyridoxine. This form of the vitamin is unstable to heat[12] and light,[13,14] especially in solution.[15]

According to Vilter and his associates[16] the approximate human daily requirement can be estimated as 2 to 3 mg. (more than 0.5 and less than 5 mg.). Intestinal synthesis, however, does occur in man,[17] feces containing appreciable quantities; whether or not the vitamin is available for absorption from this source is not known. It is essential that some estimate of the amount of active vitamin ingested daily be made.

Table I summarizes the amounts calculated in a sample hospital diet based on all analyses published except those of Rabinowitz and Snell.[6] Since most of the methods measured primarily pyridoxine, the figures for vegetables and fruits are probably fairly accurate; those for meat and milk are undoubtedly low. Fresh milk, for example, contained 0.41 mg. pyridoxal and pyridoxamine as the hydrochloride per liter, or about 0.24 mg. of the free vitamins,[6] eggs 4 mg. per kilogram, frozen fish 18 mg. per kilogram, and chicken breast and beef liver 24 mg. per kilogram, all in the fresh raw state. On this basis, if no losses occurred in cooking, 200 Gm. per day of meat and eggs should provide more than adequate amounts (3 mg.) without other foods necessarily being high in content. The losses in pyridoxine after cooking, however, may possibly be applied to other forms of the vitamin, as the aldehyde is apparently less stable. Therefore, data are not available to decide whether or not the American dietary is marginal in respect to this vitamin during seasons of the year in which canned fruits and vegetables are used widely.

Evidence for a deficiency in processed foods, however, appears in the studies of Tappan and Elvehjem,[18] who found that Army combat rations, consisting of forty-five items, were inadequate in B_6 for rhesus monkeys.* These rations, however, contained adequate amounts of all other known coenzymes but folic acid, for which the monkey has a high requirement. Army K rations were also deficient in B_6 for rats,[19,20] part of the effect residing in the ham, egg, and pork

*In this respect, reference should be made to the report by Enos, Holmes, and Beyer[51] on the extraordinarily high incidence of coronary atherosclerosis in young American soldiers killed in the Korean war, if dietary factors are involved in the disease.

loaf units, which when fresh should be good sources. Processed wheat flour was also inadequate.[21]

Therefore, from the incomplete data in the literature, it is entirely possible that the American adult is maintained on a marginal intake of this important coenzyme during periods of the year in which fresh vegetables and fruits are not available and processed foods and meats are widely used. Clinical signs of deficiency, however, apparently do not develop in so far as the skin or peripheral nerves are concerned; according to Vilter,[16] they appear only when the diet is markedly restricted.

TABLE I. CALCULATED DAILY INTAKE OF B_6 [7,36] IN REGULAR HOSPITAL DIET (2,500 CAL.)

FOOD	GM./DAY	PYRIDOXINE CONTENT (MG./100 GM.)						TOTAL MEAN INTAKE (MG.)	
		RAW		COOKED FRESH		COOKED CANNED		COOKED	
		LOW	HIGH	LOW	HIGH	LOW	HIGH	LOW	HIGH
Meat	150							0.09	0.3
Beef		0.31	0.43						
Lamb		0.21	0.38	0.10	0.13				
Stew		0.22	0.23	0.05	0.06				
Ham		0.25	0.37	0.15	0.21				
Veal		0.25	0.45	0.11	0.21				
Stew		0.32	0.34	0.09	0.10				
Salmon						0.07	0.26		
Vegetables, cooked	200			0.01	0.06*	0.014	0.10	0.03	0.2
Raw	75	0.07	0.12					0.05	0.09
Corn						0.04	0.10		
Fruit†	250	0.009	0.08			0.01	0.02	0.025	0.05
Fruit juice	200					0.007	0.027	0.014	0.05
Milk‡	720	0.003	0.011					0.022	0.078
		(0.006)						(0.042)	
Egg	50	0.02		0.01				0.005	0.005
Bread, white	75			0.004				0.003	0.003
Butter	20								
Cereal	30	0.05		0.03*				0.001	0.001
Potato	200	0.22		0.11*				0.22	0.22
Other (dressing, etc.)	40								
Total	1,935	Excluding raw fruits						0.46	0.997
		With bananas and other raw fruits						0.96	1.53

*Estimated from loss in cooking.

Note: Yeast contains 1.0 γ/Gm., stock Purina diet 2.1 γ/Gm.

†Some fruits are much higher, i.e., bananas (0.32 mg.), raisins (0.094 mg.), oranges (0.08 mg.).

‡Yeast growth method. Other reports vary from 0.067 to 0.1-0.2 mg./100 Gm. The best figure is 0.024 mg./100 Gm.[6]

These figures, most of which are based on pyridoxine content, are probably fairly accurate for vegetable sources but certainly underestimate the content of pyridoxal and pyridoxamine in animal tissues.[6] The table must therefore be interpreted as showing trends (as in cooking and canning) but not as a measure of the true concentration of B_6. No good figures on all three forms of the vitamin are available for the average diet as it reaches the table.

PYRIDOXINE AND FAT METABOLISM

A large amount of animal and hydrogenated vegetable fat is included in the American dietary as opposed to the diets of some other areas of the world

where untreated vegetable fats appear to be the predominant source. Aside from its transaminase and decarboxylase activity, one of the important functions of pyridoxine is to take part in a reaction, so far undelineated biochemically, which is concerned with the formation and utilization of unsaturated fatty acids.[22,23] Thus, linoleic acid is converted to linolenic and arachidonic is converted to hexaenoic. These conversions are stimulated in the rat, at least, by pyridoxine. It is probable that pyridoxine is involved in the synthesis of very highly unsaturated fatty acids from linoleate and linolenate.[22]

TABLE II. KNOWN FUNCTIONS OF B_6 IN FAT METABOLISM

	ANIMAL	REMARKS	REFERENCES
Enzymatic reactions involved			
Glutamic dehydrogenase	Rat liver	Enhanced by fat deficiency	24
Oxidation of butyrate and octanoate	Rat liver		26
Synthesis of arachidonate from linoleate	Rat		22
Synthesis of hexaenoate from linolenate	Rat		22
Histaminase	Rat	Indirect evidence	37
Glutamic decarboxylase	Rat brain		38
Findings in deficient animals			
Unsaturated fatty acid content reduced	Rat liver	Enhanced by fat deficiency	24
Less arachidonic acid in carcass	Rat	Percentage in fat higher	27
Biological synthesis of arachidonic acid	Rat		27
General functions			
Deposition of fat in body	Rat	Restored by fat alone	26
Fat synthesis	Rat	No change in liver lipids	26
Fat synthesis from proteins	Rat		39
Deficiencies			
Both essential fatty acids and B_6 necessary for cure of acrodynia	Rat		40
Ethyl linoleate does not spare B_6	Rat		41
Ethyl linoleate cures acrodynia	Rat		42
Hypercholesterolemia	Monkey	High cholesterol intake	25
Enzymes not affected by B_6			
Succinic dehydrogenase		Reduced in fat deficiency	24
Butyric dehydrogenase		Reduced in fat deficiency	24
Direct correlation between I_2 value of liver crude fatty acids and glutamic and butyric dehydrogenase			24

If this is so, the capacity of a pyridoxal system might be overtaxed by excessive intake of saturated or even monoethenoid fatty acids, resulting in a relative deficiency of unsaturated fatty acids, particularly if the coenzyme, pyridoxal phosphate, were present in limited amounts. On the other hand, if unsaturated fatty acids were ingested in amounts sufficient to fulfill the body's requirements, little or no deficiency might result. Furthermore, if fatty acids unsaturated in one or two positions were ingested in sufficient amounts so that further unsaturation could occur through a pyridoxal-enzyme reaction, it is entirely possible that deficiency might be borderline or not occur at all.

Tulpule and Patwardhan[24] have studied the effect of pyridoxine and fat deficiencies on enzyme systems in rat livers. Succinic dehydrogenase was not affected in pyridoxine deficiency but was reduced in fat deficiency. Glutamic dehydrogenase was significantly reduced in both pyridoxine and fat deficiencies. Butyric dehydrogenase was not affected by pyridoxine deficiency. The iodine value of crude fatty acid of liver was reduced in both fat and pyridoxine deficiency. Table II summarizes the evidence.

There are further indications that pyridoxine is important in fat metabolism. The plasma cholesterol levels of cholesterol-fed monkeys were higher in those deficient in B_6 than in the controls.[25] There was a decreased rate of oxidation of sodium butyrate and sodium octanoate by liver slices in pyridoxine-deficient rats.[23] There was less arachidonic acid in the corpses of rats on a pyridoxine-free diet.[26] Therefore, while the role of pyridoxine as a coenzyme has received greatest interest in studies on transamination and decarboxylation,[27] it appears to be essential for the formation and utilization of unsaturated fatty acids. It must be remembered that the phosphatides have unsaturated fatty acids in their molecules, particularly lecithin and cephalin, and cholesterol esters are made up largely of unsaturated fatty acids, although saturated ones are found in blood and tissues.[28] The character of the fat in lipoproteins is not yet known.

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SOLUBILITIES OF FATTY ACIDS

On the simple principle that relative insolubility of some fatty acid complexes with cholesterol, proteins, and glycerides might influence deposits in the walls of blood vessels, physical properties of the common lipids were considered.[28] Although solubilities in water or plasma are not known, to our knowledge, cholesterol esters of the long-chain unsaturated fatty acids (linoleate, linolenate) are about twenty-five times as soluble in alcohol and ten to twenty times as soluble in acetone as are the esters of the saturated fatty acids of similar length. The most insoluble esters are those containing 14, 16, and 18 carbon atoms, i.e., the common saturated myristate, palmitate, and stearate. Oleate is ten times as soluble, that containing 2 double bonds is more so, and 3 double bonds the most soluble of the long-chain esters. It is possible that this relationship holds for plasma. The solubilities of lipoprotein esters of saturated and unsaturated acids are not known.

The solubilities in water of the saturated acids themselves decrease with the length of the chain. In other solvents the unsaturated acids are considerably more soluble, influenced principally by the degree of unsaturation, and only secondarily by the length of the chain. The same general relationship holds for the glycerides. Similarly, the specific gravity or density of the fatty acids varies as the length of the chain, the longer chain acids being lighter. In general, the unsaturated fats are heavier.

DIETARY INTAKE OF FATTY ACIDS[28]

One long-recognized fact is that depot and subcutaneous fat is partly constituted of the kind of fat ingested. The fat in rats, pigs, and dogs is influenced

by the diet. Mutton tallow fed to dogs produces a hard fat, linseed oil produces a liquid one. Fats not ordinarily present in tissues can be laid down when they are fed. The unsaturated fatty acids in cod liver oil can be recovered from the bodies of rats fed this substance. Even unnatural fats will be deposited in tissues. Hogs fed peanuts or soy beans develop a "soft pork" in which the fat has a high iodine number, is partly liquid, and is therefore unacceptable to the housewife. Whether or not human tissues can be altered by the type of fat ingested has not been studied to our knowledge. Fish need unsaturated fatty acids at cold temperatures in order to remain pliable; even warm-blooded animals fed long-chain saturated acids may become stiff. The idea that saturated fatty acids might be concerned in cardiovascular disease was first suggested by Snapper to me in 1938.

An examination of the kind of fatty acids ingested as roughly correlated with the incidence of atherosclerosis is illustrated in Table III.* The impressions are most incomplete. If one takes the attitude that saturation or unsaturation of ingested fatty acids, the intake of B_6, or exposure to civilization may influence the formation of atheromata, the table is provocative.

It should be emphasized that most of the vegetable fat used in this country is hydrogenated (saturated), that fish are a minimal factor as a source of protein foods, and that butter and cream are relatively rich sources of saturated fatty acids. In Table IV are shown the iodine numbers (degree of unsaturation) of common animal and vegetable fats, the former being influenced, of course, by the dietary intake, whether immediate or remote (as in fish eaters). High-carbohydrate and -protein diets apparently promote the formation of hard body fats with a low iodine number.

Decrease in atherosclerosis in countries affected by World War II can perhaps be attributed to many dietary factors, including the type of animal or vegetable fat, eggs, protein, carbohydrate, general state of nutrition, and vitamins. Actually, the present theory, which is concerned with an abnormal saturated-unsaturated fatty acid ratio in the esters of cholesterol induced by an excessive ingestion of warm-blooded terrestrial animal fats and a marginal intake of B_6, may explain many of the geographic and temporal differences in the incidence of this disease.†

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*Ahrens and his co-workers have very recently reported that substitution of unsaturated fatty acids (corn oil) for saturated ones in isocaloric diets lowered all lipid components in plasma of human subjects; cholesterol levels did not rise until large amounts of this lipid were fed.[53]

†One striking example, unexplained by the theory developed up to this point, concerns the virtual absence of atherosclerosis and myocardial infarction in Yemenite (Oriental) Jews in Israel as compared to the "normally" high incidences in European Jews in Israel.[52] Furthermore the total plasma cholesterol levels of Yemenite Jews recently immigrating (three to five years) were considerably lower than of those of longer (over twenty years) residence; European Jews showed higher levels comparable to those found in the United States. Dietary differences have not been reported in these contiguous groups.

TABLE III. INCIDENCE OF ATHEROSCLEROSIS IN VARIOUS COUNTRIES
(Abstracted Partly from Katz and Stamler[35])

COUNTRY	GENERAL INCIDENCE	DIET	STATE OF NUTRITION	SATURATED VS. UNSATURATED FATS*[28]	B_6 CONTENT[7]	EXOGENOUS METALS
Costa Rica	Low	Low fat and animal protein, tropical fruits	Poor	Unsaturated	Excellent	0
Okinawa	Very low	Vegetables, soybeans, low fat	Good	Unsaturated	Excellent	0
China	Very low	Low fat and animal protein	Fair	Unsaturated	Good?	0
Ceylon, native	Very low	Low animal protein, high vegetable protein	Fair	Unsaturated	Good	0
Ceylon, Dutch	High	"Civilized," normal fat	Good	Saturated?	Marginal?	+?
Kenya, Africa	Low	Vegetables, low fat	Fair	Unsaturated	Good	0
Kirghizkistan	High	High meat, mares, goats' and yak's milk, little grain	Good	Saturated	Poor	0
Esquimos	Probably low	High meat, fat, low Cbh; fish and fish eaters	Good to fair	Unsaturated	Good	0
Bantus, S. Africa[13]	Low	Sorghum, peas, beans	Fair	Unsaturated	Good	0
Sweden	High	Butter, eggs, animal fats	Good	Saturated	Poor	+
U. S. A.	High	High animal fat	Good	Saturated	Poor	++
Finland	Moderate	Fish, high animal fat	Good	Both	Fair	+?

*Predominant fatty acids.

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TABLE IV. UNSATURATED FATTY ACIDS IN SOME COMMON FATS AND OILS (AFTER DEUEL[28])

FAT OR OIL	IODINE NO.	LINOLEIC (%)	LINOLENIC (%)	REMARKS
Coconut	8–10	2.6		Very saturated, 60% C_{12} or less
Cacao butter	32–38	2.0		40% oleic
Palm	53–57	0.7		Same as coconut
Butter	26–38	3.6–4.5		
Beef tallow	35–45	1.8		
Mutton tallow	32–45	4.3		
Lard	50–65			
Human fat	64	8–11		
Chicken		22		
Lard (oil)	67–82			
Menhaden	148–172			
Cod liver	135–175			
Salt-water fish*		15–26	++++	Over 75% unsaturated
Fresh-water fish		30–50	++++	Over 75% unsaturated
Olive	79–90			
Almond	93–100	17.3		
Peanut	85–100	26.0		Also arachidonic
Sesame	103–112	37.7–45.0		
Cottonseed	105–115	41.50		
Corn	115–124	56.9	5.9	
Soybean	130–138	52.0	2.3–9.0	
Alfalfa		67.5	20.8	

*Fish, an important source of food, differ in their fat composition. Fresh-water fishes contain 20 per cent palmitic and a very high unsaturated acid content, while marine fish contain more of the longer chain acids (C_{20}, C_{22}). Unsaturation of both types is high. Marine mammals have a marine type of fat.

HEAVY METALS

It is suggested by Snell[27] that trivalent metal is necessary for the transamination reactions in which pyridoxal plays a part. A metal is also essential for other functions of the coenzyme. It is not known, however, whether a metal is or is not necessary for the enzymatic reactions concerned in fat metabolism. There is evidence, however, that certain agents which bind metals are antagonistic to pyridoxal. For example, convulsions induced by semicarbazide, a metal-binding and a carbonyl reagent, can be prevented by pyridoxine.[29] Vitamin B_6 is affected by isonicotinic acid isopropyl hydrazide; patients and animals given this drug, a metal-binding agent by virtue of its hydrazine group, excrete excessive amounts in the urine.[30,31] It is possible that on binding the metal, pyridoxal is released therefrom; however, a direct combination may take place between B_6 and the hydrazine, which is then excreted as a conjugate.[30] Furthermore, certain decarboxylases requiring B_6 as coenzymes are inhibited by hydrazines.[32,33]

Many "abnormal" trace metals are present in American human tissues. The accurate and extensive studies of Tipton and her co-workers[34] have shown that certain organs from "normal" persons dying accidentally contained relatively large quantities of "abnormal" metals (Table V), in some cases as much

as or more than of the "essential" ones (manganese, cobalt, copper, zinc, and molybdenum). For example, in the liver, an organ concerned with fat metabolism, there was more cadmium, aluminum, and lead than manganese. In the kidney, an organ which may be concerned indirectly with fat metabolism but which is directly involved in the hypertensive process, there was a very high concentration of cadmium (33.1 mg. per kilogram; range 12.2-54.4), one-half as high as that of essential zinc (67.2 mg. per kilogram; range 34.4-130); lead, aluminum, and tin occurred in larger amounts than manganese. In the adrenal there was more aluminum and almost as much lead and cadmium as copper. In the lung there was more aluminum than zinc, as well as large amounts of titanium. Little or no cobalt, an essential metal, was demonstrated, although nickel was found in all tissues,* and chromium occurred in concentrations about equal to molybdenum. The affinities of some tissues for certain metals and the relatively even distribution of others throughout all organs are provocative of thought.

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The role of trace metals in fat metabolism has not been well studied, but there are a few suggestive bits of evidence. Manganese has been considered a lipotropic agent in that fatty livers resulted from its deficiency; an interaction between the metal and choline was indicated.[44] Chromium increased by 150 per cent the formation of both cholesterol and fatty acids from C^{14} -labeled acetate in rat livers; manganese increased it by 125 per cent, while vanadium depressed the synthesis considerably. Little or no effect was obtained by other transitional metals with atomic numbers 22 to 30 (titanium to zinc).[45] Ethylenediamine tetraacetate, a metal-binding agent, prevented cholesterolosis of the liver in cholesterol-fed rabbits.[46] Hydralazine, a metal-binding agent, lowered plasma cholesterol rapidly in human subjects.†[47] This drug appeared to lessen the abnormal trace metals found in hypertensive human urine, particularly chromium.[48]

The idea that one trace metal can displace another in a biologic system and inactivate it has at least two experimental counterparts. Zinc, essential for carbonic anhydrase, can be replaced by copper and probably cadmium, which inhibit the enzyme. Tyrosinase, which requires copper, is inactivated by gold, silver, and mercury, which apparently displace the copper on the protein molecule. Furthermore, Williams[49] has suggested that the metals acting as less specific catalysts are active in order of their strengths of chelation according to atomic number; i.e., $Mn < Fe < Co < Ni < Cu > Zn$.[49] There are many enzymes in which metals play a part, e.g., peptidases, carboxylases, phosphatases. When certain metals inhibit an enzyme system and others do not catalyze, sulfhydryl is probably bound. Other examples may exist, but information is not available at the present time to permit speculation on where they may act, as on pantetheine, for example. Such speculations concern the inactivation

*It is interesting that nickel catalysts are used in the commercial hydrogenation of edible vegetable fats.

†Curran has further reported that 8-hydroxy-quinoline decreases the incorporation of C^{14}-carboxyl-labeled acetate into cholesterol by surviving rat liver while ethylenediamine tetra-acetate increases this incorporation.[54] In eight human subjects studied by us, the calcium salt of this latter chelating drug, given intravenously, rapidly but temporarily lowered plasma cholesterol levels from a mean of 220.3 to 144.6 mg. per cent.

TABLE V. TRACE METALS IN MAN (AFTER TIPTON AND ASSOCIATES[34b])

ORGAN	ELEMENTS IN AVERAGE CONCENTRATIONS GREATER THAN 1.0 MG. PER KG. (WET WEIGHT)										
	ESSENTIAL				ABNORMAL						
	Mn†	Cu†	Zn†	Mo	Ti*	Cr*	Ni	Cd	Sn*	Pb†	Al†
Adrenal		1.69	15.3					1.24		1.04	4.41
Aorta		1.96	20.2					1.09		1.05	*9.09*
Bladder		3.40	16.6								2.53
Brain		*10.63*	16.8					0			3.55
Heart		4.09	49.2					(1.74)			2.51
Intestine		2.33	20.2					1.21			2.68
Kidney		2.76	*67.2*					*33.1*		1.27	1.80
Liver	*1.13*	*10.57*	*68.4*	*1.62*				3.60		*2.04*	2.55
Lung		4.49	18.3		*7.65*			1.73		1.21	*30.8*
Muscle		1.53	*69.9*					(1.78)			3.01
Pancreas		3.00	41.0					2.10		1.32	2.67
Prostate		4.79	*155*		*1.51*			(1.55)			5.53
Spleen		*8.67*	22.3					(1.96)		1.33	3.34
Stomach		3.70	27.0					1.14			4.86
Testis		2.10	13.8					(1.31)			3.87
Thyroid		3.50	36.6					2.08	*1.00*		5.12

CONCENTRATIONS GREATER THAN 0.3 AND LESS THAN 1.0 MG. PER KG.

Adrenal					0.52				0.34		
Aorta				(0.53)	0.75				0.42		
Bladder						0.42		(0.93)		0.39	
Brain	0.40					0 36			0.55	0.31	
Heart									0.36	0.98	
Intestine					0.39		0.33		0.54	0.78	
Kidney	0.43			*0.63*					0.48		
Liver	—			—			0.32		0.65		
Lung	*0.58*				—	*0.72*	0.47		0.95		
Muscle				0.41	0.48		0.40		0.51	0.71	
Pancreas	*0.74*						0.32		0.53		
Prostate				(0.36)	—		0.48		0.74		
Spleen	*0.52*				0.31	*0.63*	0.72		0.41		
Stomach	0.37				0.59		0.49		0.41		
Testis						0.39	0.67			0.67	
Thyroid	*0.48*				0.37	0.42			—	0.50	

Figures in italics are 5 times the mean of the lowest organ. The figure in parenthesis indicates the presence in less than one-half the samples.

*Metal found in over 90 per cent of samples. Cd was in 70, Mo in 72, Ni in 76 per cent.

†Metal found in all samples.

These analyses were made by arc spectrography employing indium as an internal standard. Tissues were from 24 persons dying instantaneously in New York, Chicago, and Memphis. Only those metals present in sizeable concentrations and found in practically all tissues are shown. Ag was found in smaller concentrations than 0.3 mg./kg. wet weight and was almost universally distributed; B and Au were sometimes found, Bi less frequently, Tl once, and Co, curiously enough, was present in only five cases. Ga was in most lung tissue. Possible metalloenzymatic competitors and inhibitors include Cd for Zn, Ag and Au for Cu, Ni for Co, and Cr for Mn; perhaps, however, some of those listed as "abnormal" are actually "essential." Note the affinities for certain tissues.

of part of the available B_6 by an exogenous trace metal displacing the essential metallic component of the anzyme-coenzyme system. In our laboratory, for example, Perry and his co-workers have found that cadmium, of nine metals tested, was the most potent inhibitor of DOPA decarboxylase, a pyridoxal enzyme.[32]

DISCUSSION

The trend of incidence by age of atherosclerosis (and arterial hypertension) is consistent, among other factors, with the gradual accumulation in the body of some exogenous substance over many years. The virtual absence of atherosclerosis and hypertension in countries where there is little "civilization" suggests that while dietary factors may be important, other influences may also play a significant role. If human fat can be influenced by the dietary intake, the markedly different solubilities of cholesterol esters made of saturated and unsaturated fatty acids provide a possible reason for atheromatous deposits in arterial walls. The role of B_6 in the formation of unsaturated fatty acids, and therefore soluble ones, seems clear. The American diet may possibly be marginal with respect to this vitamin during certain seasons of the year. Not only may the diet differ in its fat and vitamin content, but the inhabitants also differ in their exposure to trace metals in canned and processed foods, in the products of petroleum combustion, and water piped through metal pipes,* for example. The presence of chromium, cadmium, nickel, aluminum, tin, and lead in human tissues may or may not interfere with essential metalloenzymes. One or more could "condition" a B_6 deficiency by competing with a normal metal in the pyridoxal complex. The propensity of cadmium to displace zinc, and the propinquities of chromium and nickel to other "essential" transitional elements in the periodic table place these metals under suspicion.

Among other stresses, "civilization" can impose upon the human organism three: exposure to exogenous trace metals in abnormal amounts, excessive dietary intake of saturated fatty acids, and a marginal intake of vitamin B_6. Since these three factors may be interrelated biochemically, a partial explanation for the pathogenesis of atherosclerosis may be advanced. Absence of two of these stresses might reduce the prevalence of the disease. Other factors, such as intra-arterial pressure,† and ingestion of cholesterol may thus be of secondary pathogenetic importance. While intimal injury from other causes might initiate lesions, a sustained or intermittent deficiency of B_6 could possibly also produce them, through disturbed metabolism either of amino acids or of fats.[50]

Directions for research along these lines are obvious. First, a comparison of trace metal content of tissues from "uncivilized" areas of the world with those found in this country may suggest which are linked to "civilization." Prolonged animal experiments can give valuable clues as to accumulation and

*Prime Western zinc, the grade used for galvanizing, contains about 0.75 per cent cadmium. Most water pipes in dwellings in the United States are of galvanized iron.

†It is not beyond the bounds of reason to consider that deficiency of pyridoxal phosphate may provide a common biochemical denominator between some forms of arterial hypertension, through its effect upon transamination, and atherosclerosis, through its effect upon fat metabolism; abnormal trace metals may influence both systems.

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toxicity in terms of cardiovascular diseases. Second, the atherogenic influences of fats and sterols need study from the viewpoint of saturated-unsaturated fatty acid ratios, both with and without trace metals. Third, the part which these metals play in fat metabolism deserves further elucidation. Fourth, the fundamental biologic role of pyridoxal phosphate, with reference to basic biochemical reactions, storage, utilization, and requirements, needs examination. Fifth, clinical experiments in the light of this new knowledge, instead of in the present obscurity, may provide means for reversing some of the lesions.

SUMMARY OF THE VARIOUS FACTORS CONCERNED

Atherosclerosis has been produced in the monkey and hypertension in the rat by deficiency of vitamin B_6. The possibility exists that human atherosclerosis and/or hypertension is influenced by B_6 deficiency. In support of this thesis are the following observations:

1. B_6 is concerned with the formation and utilization of unsaturated fatty acids and deficiency can cause intimal lesions.

2. A diet high in saturated fatty acids might result in (a) an excess of less soluble esters of cholesterol, (b) a physical change in the character of body fat and lipoproteins, especially if a pyridoxal-enzyme system were overloaded.

3. The American diet is probably marginal in B_6 with reference to some cooked and processed foods.

4. The American human body contains many "abnormal" trace elements, several of which could compete for an essential metal in a pyridoxal-enzyme system and reduce the amount available for metabolism, thus producing a conditioned deficiency.

5. The combination of marginal vitamin intake and high saturated fat loading with or without trace metal competition could result in an abnormality of fat metabolism such as occurs in atherosclerosis, with an alteration in the ratio of saturated to unsaturated fatty acids, and possibly a further alteration in the physical properties of some phospholipids, lipoproteins, and cholesterol esters.

There are many unknown links in the chain of reactions presented by this hypothesis. As a working system evolved from available information, however, it may help to point the way toward investigative work aimed at elucidation of pathogenetic factors. There is little or no experimental evidence against the hypothesis; in fact, most of what is known appears to fit. The pyridoxal-enzyme system may be the "other factor" in atherogenesis so often postulated. Proof or disproof awaits facts backed by clinical experiments.

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THE FATE OF URIC ACID IN THE NORMAL AND GOUTY HUMAN BEING

JAMES BUZARD, PH.D.,* CHARLES BISHOP, PH.D., AND JOHN H. TALBOTT, M.D.

BUFFALO, N. Y.

From the Departments of Biochemistry and Medicine and the Chronic Disease Research Institute of the University of Buffalo School of Medicine, and the Buffalo General Hospital

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URICOLYSIS is defined as the process of uric acid breakdown and usually is applied to a biologic phenomenon. Uricolysis is believed to proceed in most mammals since uricase, an enzyme known to facilitate this process, is present in the tissues. Furthermore, allantoin rather than uric acid itself is the chief excretory product. Because uricase has never been demonstrated unequivocally in the tissues of man and because man excretes allantoin rather than uric acid, it has become generally accepted that uricolysis does not occur in man. When N^{15} uric acid has been injected intravenously into normal human subjects, the recovery as urinary uric acid has been reported to be from 60 per cent to nearly 100 per cent.[1-3] The inability to recover completely the injected dose does not demonstrate the occurrence of uricolysis, but the finding of small but significant labeling in the urinary urea and ammonia[1,4] does indicate the breakdown of uric acid somewhere in the body. The general procedure for carrying out uric acid studies with N^{15} uric acid has been to inject intravenously 25 to 100 mg. of labeled uric acid. Since the miscible pool of body uric acid has been determined to be approximately 1,000 mg.,[1-3] these small doses would not appreciably alter the prevailing homeostasis. Nor could they induce really significant labeling of the urinary urea and ammonia because of the large dilution factors involved in the formation and excretion of these compounds. Increasing the size of the dose of injected N^{15} uric acid is the only obvious procedure to determine whether labeled urea can arise from labeled uric acid. Such a study was performed by Wyngaarden and Stetten[5] in which they injected intravenously 1,000 mg. of N^{15} uric acid. They observed a regularly ascending pattern of labeling of the urinary urea up to 2.5 days and a regular decline thereafter.

The data in this paper were submitted by James Buzard to the Graduate School of Arts and Sciences of the University of Buffalo in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Biochemistry.

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*Present address: Biology Division, Eaton Laboratories, Inc., Norwich, New York.

It has been known for years[6] that uric acid enters the gastrointestinal tract via the bile and gastric juice. There it could be decomposed by the intestinal flora to smaller catabolities. To rule out such a possibility, Wyngaarden and Stetten[5] repeated their experiment except that the subject received phthalysulfathiazole before and during the experiment to suppress the activity of intestinal organisms. The findings were virtually identical with the first study. These authors concluded: "These results are taken as proof of the occurrence of uricolysis in normal man and as indication that the intestinal flora does not make a major contribution to this process." Earlier in the same communication, the authors noted that uric acid in alkaline medium, specifically in sterile duodenal juice at pH 8.4, has been shown to undergo rapid destruction. It would seem reasonable that intravenously injected N^{15} uric acid, especially at a high dose level, could be secreted into the gastrointestinal tract and be broken down to N^{15} urea and other catabolites by virtue of the medium prevailing therein and with no necessity for floral action. In such a situation, uricolysis occurs in the human being, but it should be pointed out that such uricolysis takes place in the gastrointestinal tract rather than within the body proper. It is important to mention this distinction since the metabolic defect causing gout might be related to failure of a normally occurring uricolysis. This would almost certainly be an alteration within the body tissues per se rather than a change within the gastrointestinal tract.

It is the object of the present paper to show that: (a) with small doses of N^{15} uric acid, injected intravenously, only a small percentage of the dose is converted to urinary urea or ammonia in the normal subject: (b) most of the remainder of the dose not recovered as urinary uric acid can be accounted for as fecal nitrogen: and (c) N^{15} from injected uric acid is secreted in the bile. The irreconcilable difference between the present work and that of Wyngaarden and Stetten is that, for technical reasons, uricolysis can be demonstrated only when the dose of injected uric acid is very large, and that under more physiologic conditions, the absence of uricolysis can be established only by implication.

It will also be noted in this study that the recovery of injected N^{15} uric acid in the gouty individual is less than in the normal individual. This indirectly argues against a failure of uricolysis as the cause of gout since in that case the recovery should be higher in the gouty individual than in the normal.

METHODS

Uric acid labeled with N^{15} was synthesized by the method of Cavalieri, Blair, and Brown[7] and injected as previously described.[8] Urine, and stools when required, were collected ad libitum and pooled into appropriate time periods. Uric acid in urine was determined by the isotope dilution method.[8] Urea and ammonia were determined by the urease-areation method.[9] Total nitrogen was estimated by the modified Kjeldahl procedure of Hiller, Plazin, and Van Slyke.[10] Determinations of N^{15} were performed on the Consolidated-Nier isotope ratio mass spectometer after the method of Sprinson and Rittenberg.[11]

EXPERIMENTAL AND RESULTS

Experiment 1.—Subject J. B., a 24-year-old white, normal man, was placed on a low protein diet* and twenty hours thereafter was intravenously injected with 98.2 mg. of uric acid containing 29.9 atom per cent excess N^{15} (0.697 mM. N^{15}). The low-protein diet was continued for twenty-four hours after the injection. The object of the diet was to reduce the dilution effect of endogenous urea. Urinary urea, ammonia, and uric acid were determined quantitatively and for N^{15} concentration.

While the anticipated amount of N^{15} was recovered in the urinary uric acid (72.0 per cent), only 3.4 per cent was recovered in the urinary urea and ammonia during the first seventy-two hours. It was of interest to note that neither the urea nor ammonia fractions contained N^{15} in regular sequence, and this suggested that intestinal decomposition of uric acid might account for the N^{15} appearing in these fractions.

To obtain data on fecal excretion, Subject J. B. was again injected, four months after the first study, with 75.0 mg. of 16.42 atom per cent excess N^{15} uric acid (0.288 mM. N^{15}). Urine was collected and pooled appropriately. Stools were collected, homogenized, and diluted to appropriate volumes with dilute HCl. From Fig. 1*a* it can be seen that the N^{15} concentration of the fecal nitrogen reached a maximum on the second day and declined regularly. This coincides roughly with the maximum at 2.5 days in urinary urea N^{15} in Wyngaarden and Stetten's paper. Cumulation of the N^{15} excreted showed that 77.7 per cent of the dose was excreted as urinary uric acid in nine days, while 16.0 per cent of the dose was excreted as fecal nitrogen in six days. The recovery was thus 93.7 per cent.

The same study was repeated one year later. This time 49.7 mg. of uric acid containing 11.70 atom per cent excess N^{15} (0.138 mM. N^{15}) was injected. Six days later the urinary uric acid had returned to its normal isotope concentration and the subject had excreted 75.2 per cent of the dose in the urinary uric acid. The fecal nitrogen again displayed a maximum isotope concentration on the second day. The feces contained a total of 19.4 per cent of the injected N^{15}, to give a total recovery of 94.6 per cent of the dose.

At this time a patient who had just undergone a cholecystectomy became available for study.† The patient, L. M., a 66-year-old white woman, was injected with 50.3 mg. of 16.15 atom per cent excess N^{15} uric acid (0.193 mM. N^{15}). Three days after operation, bile was collected through a T tube which had been inserted in the common duct. Within seven days after the injection, this subject had excreted 70.9 per cent of the injected isotope in the urinary uric acid. The fecal N^{15} concentration reached a maximum on the second day and was related to the concentration of N^{15} in the bile (Fig. 2). Since it was not possible to collect the bile quantitatively, the recovery of the isotope in the bile or feces could not be determined quantitatively.

*This diet was essentially a vegetable diet designed to avoid protein foods. During the first twenty-four hours of the experiment the urinary urea excretion was approximately 15 Gm. and the urinary ammonia excretion was 0.140 Gm.

†We would like to thank Dr. Richard Egan of the Department of Surgery of the Buffalo General Hospital for his assistance in obtaining the surgical case studied.

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Thus far it had been shown that in the normal subject about 94 per cent of the intravenously injected dose of N^{15} uric acid could be accounted for on the basis of urinary uric acid and fecal nitrogen. The remaining amount recovered in urinary urea and ammonia would nearly quantitate the recovery except that the error in these determinations is great because of the low isotope concentration. The urea and ammonia data would therefore prove little by themselves, but are merely supportive.

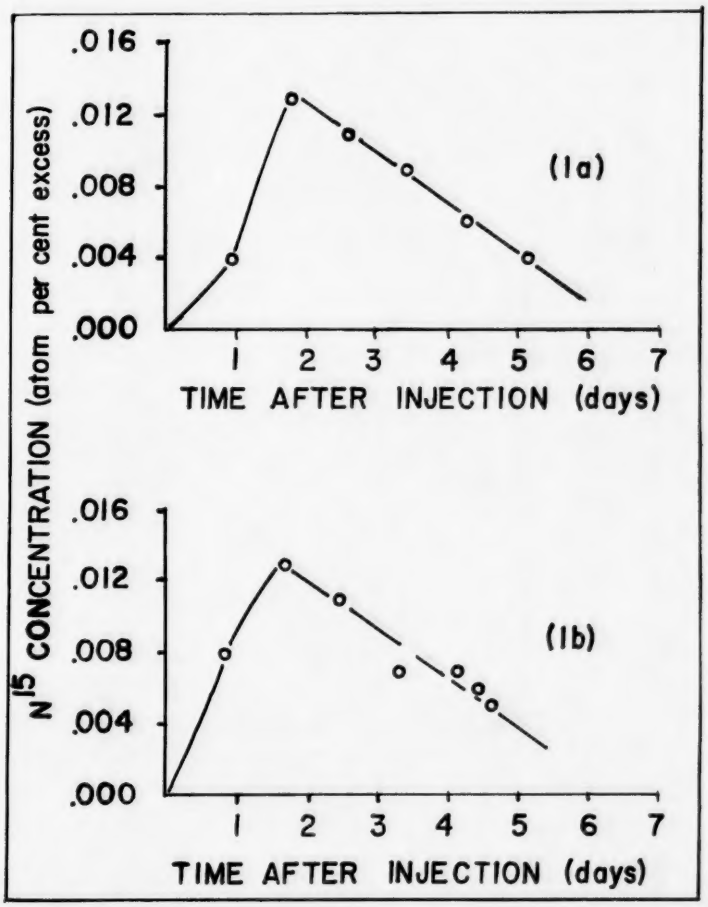

Fig. 1.—The excretion of N^{15} in the fecal nitrogen after intravenous injection of N^{15} uric acid in: (*a*) normal subject, J. B., and (*b*) gouty subject, G. S.

It should be emphasized once more that the dose size of injected uric acid was relatively small in relation to the size of the pool of miscible uric acid. The doses of Wyngaarden and Stetten were, on the other hand, approximately equal to the size of the uric acid pool. In the latter situation the concentration of N^{15} uric acid in the blood must have been increased markedly, thus facilitating

the secretion of labeled uric acid into the bile and intestine. The recovery of appreciable amounts of labeled urea in the urine after such experiments would not seem to prove significant uricolysis in the tissues of the normal human being, even though such rigorous methods are the only means available to raise the urea labeling to an unequivocal level.

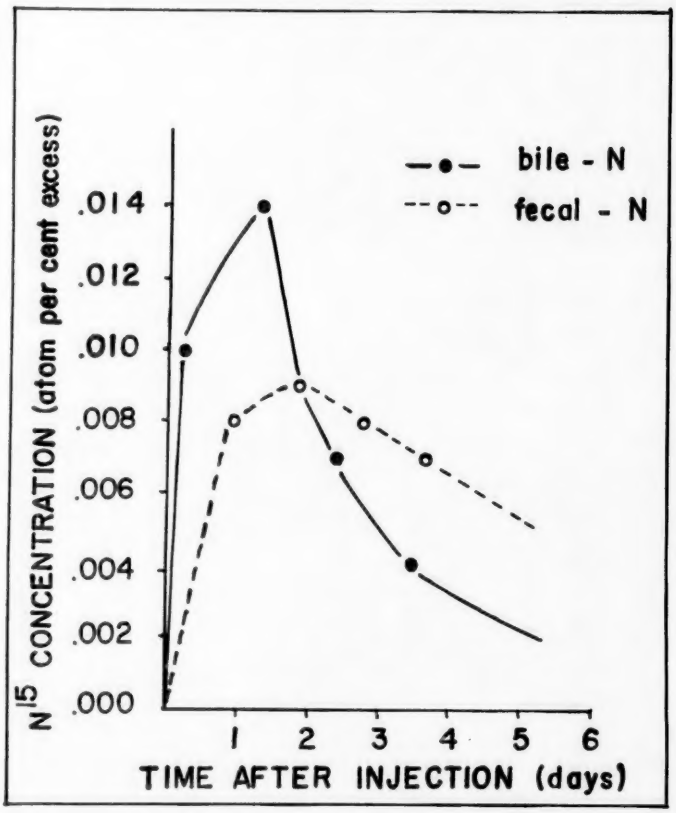

Fig. 2.—The excretion of N^{15} in the fecal and bile nitrogen after intravenous injection of N^{15} uric acid into a patient with a T tube in the common bile duct.

Gouty subjects were studied next. Subject G. S., a 64-year-old white man with a thirty-eight-year history of gout but with no obvious tophi, was hospitalized. After a period of adjustment to the dietary regimen,* this subject received 44.2 mg. of 14.15 atom per cent excess N^{15} uric acid (0.170 mM. N^{15}) by intravenous injection. Within eight days 52.1 per cent of the dose was

*All gouty subjects in this study were hospitalized and placed on a standard low-purine diet with a moderate nitrogen intake. The details of the diet varied slightly from patient to patient because some studies were performed at the Buffalo General Hospital and some at the Chronic Disease Research Institute. Drugs administered were limited to maintenance doses of colchicine (usually 2 × 0.5 mg. per day) except in the case of G. S., where medication for a cardiac condition was required.

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recovered as urinary uric acid. From the pool size (2,159 mg.), turnover rate (0.437 pools per day), and mean daily excretion (496 mg. per day), it was calculated that the per cent of the turnover that was excreted was 52.6. This figure agrees with the per cent dose recovered.

It must be remembered that in the subject with tophaceous gout, only the miscible pool of uric acid is measured by this technique. It is doubtful that the method employed gives any true indication of the quantity of uric acid incorporated into solid tophaceous deposits of uric acid.

A tophaceous gouty subject, E. Sch., was injected with 50.0 mg. of isotopic uric acid. Within eight days he had excreted 53.9 per cent of the dose. From his pool size (2,796 mg.), turnover rate (0.460), and mean daily excretion (823 mg. per day), it was calculated that the per cent of the turnover excreted was 64.5. It is conjectured that the disparity between the theoretical and actual recovery may be due to isotopic uric acid "lost" to the tophi through exchange of isotopic for nonisotopic uric acid.

Another gouty subject, F. B., was injected with 61.1 mg. of isotopic uric acid. His pool size was calculated to be 1,793 mg. and his turnover rate, 0.322 pools per day. The recovery was 51.3 per cent. The per cent of turnover excreted was 59.0.

Since the urinary uric acid accounted for only one-half of the injected dose in these three gouty subjects, it seemed desirable to examine other routines of disposal. Subject G. S. was again hospitalized and placed on a low-purine, moderate-nitrogen diet. After one month he was injected with 78.4 mg. of 16.15 atom per cent excess N^{15} uric acid (0.301 mM. N^{15}). Urinary uric acid and fecal nitrogen were determined. From Fig. 1*b* it can be seen that the fecal nitrogen reached its maximum N^{15} concentration on the second day and that the curve is nearly identical with that of the normal subject in Fig. 1*a*. Within eleven days 40.2 per cent of the injected dose had been recovered as urinary uric acid and within seven days 26.5 per cent had been recovered in the fecal nitrogen. The total recovery was thus 66.7 per cent.

Another gouty subject, D. F., was a white man with a ten-year history of gouty arthritis and extensive tophaceous deposits. He was injected with 42.5 mg. of 17.36 atom per cent excess N^{15} uric acid (0.176 mM. N^{15}). Within twelve days this subject had excreted 37.8 per cent of the dose as urinary uric acid and 37.5 per cent as fecal nitrogen. The latter again showed a maximum isotope concentration on the second experimental day. The total recovery in this study was 75.3 per cent.

The last gouty subject, J. T., a 67-year-old white man with an eight-year history of gouty arthritis and extensive urate deposits, was hospitalized for one month. He was injected subsequently with 61.7 mg. of 11.70 atom per cent excess N^{15} uric acid. In addition to urinary uric acid and fecal nitrogen, the urinary urea and ammonia were also examined for isotope content. Within eight days this subject excreted 34.4 per cent of the injected dose as urinary uric acid, 24.8 per cent as fecal nitrogen, and 8.9 per cent as urinary urea and ammonia (combined).

DISCUSSION

The foregoing experiments show that N^{15} from intravenously injected N^{15} uric acid is eliminated in the bile and appears in the fecal nitrogen, thus confirming previous observations.[6] In the normal individual nearly all of the injected dose can be accounted for as urinary uric acid plus fecal nitrogen. The experiments were not designed to prove significant labeling of the urinary urea since the dose given was small. It seemed to us unnecessary to attempt to demonstrate marked conversion of uric acid to urea in the normal subject since most of the injected N^{15} uric acid can be accounted for otherwise. Furthermore, the conversion can only be proved under distinctly unphysiologic conditions.

The maximum concentration of N^{15} in the urinary urea in the experiments of Wyngaarden and Stetten appears shortly after the feces show maximal N^{15} enrichment as noted in the present studies. The authors of this paper suggested that this is more than a coincidence. The data at hand so far do not exclude the possibility of uric acid breakdown in the body but such a postulation is not required to explain the findings to date.

Barring some difference in tissue properties, the fact that the gouty individual has more uric acid in his body than the normal individual implies that he makes uric acid too fast or disposes of it too slowly. In the latter case one might speculate that the slowing down or stopping of a normal disposal pathway could lead to uric acid accumulation in the gouty subject. That uricolysis could be such a pathway seems unlikely since it apparently plays no important role in uric acid disposal in the normal individual and because, if this were the defect in gout, one would expect higher recovery of the dose in the gouty subject.

In the classical study by Folin, Berglund, and Derick[12] in which 1 to 2 Gm. of uric acid was injected intravenously, the recovery in the urine ranged from 28 per cent to 101 per cent in twelve normal subjects and 15 to 94 per cent in eight gouty subjects. The medians of these two distributions are 69 and 30 per cent, respectively.

In the present studies, the recovery of N^{15} uric acid is uniformly lower in the gouty subject than in the normal subject. Empirically this coincides with the lowered turnover rate in the gouty subject. Because of this lowered turnover rate the gouty subject does not dispose of an injected dose of N^{15} uric acid as rapidly as the normal subject. This allows more time for uric acid to be taken up by processes which might not normally be significant. The exchange of isotopic for nonisotopic uric acid in solid phase urate is another way for temporary disposal of labeled uric acid. The lower recovery in the gouty subject may be due to such cases, or it may represent a significant pathologic departure of which we have no intimation at present. The latter case may be easier to prove than the former.

It has been suggested not infrequently that gout may be related to some degree of kidney dysfunction. All subjects, both normal and gouty, used in the present study appeared to have normal kidney function on the basis of blood urea levels and phenolsufonphthalein tests. It is true that if the ability to excrete labeled uric acid were impaired in the gouty subjects, then more of

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the dose would be left to be excreted in the feces. We suggest that the gouty subjects here are indeed unable to excrete the injected dose of labeled uric acid via the urine as rapidly as the normal subjects, but that this relative failure of excretion is mathematically related to the larger pool size and slower turnover rate of the gouty subjects and not to kidney function per se.

SUMMARY

A normal subject was intravenously injected on three occasions with a relatively small dose of N^{15} uric acid. The recovery of N^{15} as urinary uric acid was 72 to 78 per cent and as fecal nitrogen was 16 to 19 per cent. Less than 4 per cent was recovered as urinary urea and ammonia. When N^{15} uric acid was injected into a normal subject after cholecystectomy, N^{15} was found in the bile collected from a T tube in the common duct. The recovery of intravenously injected N^{15} uric acid as urinary uric acid in six gouty subjects was less than in the normal subject (34 to 54 per cent). In the three of these subjects who were thus studied, the recovery of N^{15} as fecal nitrogen was somewhat above normal (25 to 38 per cent).

It is concluded that in the normal subject uric acid is mainly disposed of as urinary uric acid or fecal nitrogen. This cannot be said for the gouty subject. Whether this inability to recover completely the injected dose of uric acid in these two fractions in the gouty subject is due to an artifact of the experimental conditions or to a novel feature of metabolism cannot be decided with the present data.

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AN EPIDEMIOLOGIC LOOK AT THE PROBLEM OF CLASSIFICATION IN THE FIELD OF ARTHRITIS*

SIDNEY COBB, M.D., M.P.H., WILLIAM R. MERCHANT, M.D., AND JOSEPH E. WARREN, M.D.

PITTSBURGH, PA.

From the University of Pittsburgh Schools of Public Health and Medicine

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DURING the past year we have had a most interesting and thought-provoking experience, for we have been examining persons drawn from the general population of the Arsenal Health District of Pittsburgh as part of an investigation into survey techniques that might be applicable in the field of arthritis. We are working with a sample of 10,000 persons in 3,000 households. A subsample has been selected for examination from which we have already examined about 600 persons.

We started our examinations rather expecting to see people with diagnosable disease fairly regularly. However, of the 372 persons whom we felt had genuine rheumatic complaints, only one case in eight would fit a "classical" description of one of the rheumatic diseases. Most of these people had not consulted their family physicians about these complaints, let alone sought consultation with a specialist. We believe, therefore, that we have encountered a distribution of severity very different from that which is seen in usual clinical practice.

To show the nature of this problem, we have devised a charting system which is necessarily abbreviated for presentation. It can, of course, be expanded to any desired degree by extending or subdividing the observational categories. Table I shows three cases that are easily recognized as "classical" types. The following points are covered:

1. Evidence of rheumatoid arthritis by x-ray film.
2. Evidence of joint inflammation.
3. Systemic manifestations including fatigue, elevated sedimentation rate, weight loss, anemia, iritis, and nodules.
4. Morning stiffness, a most important symptom.
5. Joint pain.
6. Evidence of degenerative changes in joints on physical examination.
7. Evidence of degenerative changes by x-ray film.

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TABLE I. THREE WELL-DEFINED CASES OF RHEUMATIC DISEASE

CASE NO.	SEX	AGE	RA BY X-RAY	JOINT INFLAM.	SYSTEMIC MANIFEST.	MORNING STIFFNESS	JOINT PAIN	JOINT DEGENERATION	
								P.E.	X-RAY
R. A. 10801–03	F	28	+ + + +	+ + + +	+ +	+ +	+ +		
D. J. D. 12508–02	F	83					+	+ + + +	+ + + +
Mixed 23007–01	M	71	+ + +	+ + + +	+	+ +	+ + +	+	+ + +

In each column, the presence and extent of the manifestation in question is graded from zero to ++++. For example, + joint inflammation means a history of joint swelling at some time in the past, while ++++ joint inflammation means that at least three joints were found to be swollen on examination.

The first case is a 28-year-old woman whose extensive rheumatoid arthritis could be recognized as she walked in the door. The second is an 83-year-old woman with extensive degenerative changes in her joints that caused her mild, intermittent, vesperal pain. The third is a 71-year-old man who was found to have pain, tenderness, and swelling in the shoulders, wrists, and sternoclavicular joints. X-ray showed rheumatoid destruction in the wrists, a "bamboo" spine, and osteophytes on the terminal interphalangeal joints and on the knees.

We should take a good look at these obvious cases, for they are the landmarks that will guide us in our exploration of intergradations on the next three tables.

Table II is headed by the case of classical rheumatoid arthritis that we saw at the top of Table I. Below this we see another young woman whose trouble began after her second pregnancy with joint pain, morning stiffness, and fatigue. She now gives a history of swelling, redness, and heat in the proximal interphalangeal joints, and early osteoporosis in the hands is demonstrable by x-ray. Below this, we see three cases with manifestations of disease decreasing in frequency and severity, and finally, at the bottom is a man with morning stiffness only.

We present this interesting grouping of cases under the title of rheumatoid disease, not because we have any incontrovertible evidence for this as one disease process, but simply because we cannot decide where one should stop counting if one wants to state the prevalence of rheumatoid arthritis. We believe that there are no sharp lines of clinical demarcation anywhere between the top and bottom of this chart. Later studies of frequency and age distributions of various segments of this gradient may give us clues as to how to make significant di-

visions. It is interesting to note that the "classical" case, at the top, and the individual with morning stiffness only, at the bottom, are relatively rare types. In fact, for every case of rheumatoid arthritis demonstrable by roentgenogram, there are in our sample population thirty to fifty persons with morning stiffness and joint pain. This gradient needs to be described more fully to ascertain the frequency of various symptom patterns, and whether or not there is a tendency for individuals to progress in a predictable fashion from one severity classification to another.

TABLE II. THE GRADIENT OF RHEUMATOID DISEASE

CASE NO.	SEX	AGE	RA BY X-RAY	JOINT INFLAM.	SYSTEMIC MANIFEST.	MORNING STIFFNESS	JOINT PAIN	JOINT DEGENERATION	
								P.E.	X-RAY
10801-03	F	28	+ + + +	+ + + +	+ +	+ +	+ + +		
25504-02	F	33	+	+ + + +	+	+ +	+ + + +		
32710-04	F	18		+	+	+ +	+		
32710-02	F	43			+	+ + +	+ +		
12115-03	F	11				+ +	+		
26208-01	M	50				+			

Pending better descriptions, however, one can readily see what a serious problem this gradient poses for those who wish to count cases, be they interested in epidemiology or in therapeutic trials. For example, simply by taking a broader definition of what constitutes osteoporosis, we could easily double the number of cases per thousand population that we might report as having characteristic x-ray findings of rheumatoid arthritis. This sort of unsolved problem in definition stops us from making any reports on disease prevalence at this time. Similarly, one group taking an ever so slightly broader view of the lower limit of "classical" rheumatoid arthritis could include for therapeutic trial a group of cases with a very different prognosis from those included by a group taking a narrower view. Although the detailed statistical analysis of this problem is not yet accomplished, our observations would lead us to believe that seemingly minor differences in definitions will make large differences in the number of cases found in a given category.

Table III shows that a similar gradient exists in the area of degenerative changes in joints. At the top is our "classical" case of degenerative joint dis-

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ease and below it are cases with decreasing severity of degenerative changes. It is difficult to decide at what point one should stop talking about disease and speak instead about degenerative changes compatible with the patient's age.

TABLE III. THE GRADIENT OF JOINT DEGENERATION

CASE NO.	SEX	AGE	RA BY X-RAY	JOINT INFLAM.	SYSTEMIC MANIFEST.	MORNING STIFFNESS	JOINT PAIN	JOINT DEGENERATION	
								P.E.	X-RAY
12508–02	F	83					+	+ + + +	+ + + +
27503–05	F	50						+ +	+ + +
10905–01	M	63						+	+ + +
12205–01	M	52							+ +
10509–01	M	51							+

TABLE IV. WHAT IS DEGENERATIVE JOINT DISEASE?

CASE NO.	SEX	AGE	RA BY X-RAY	JOINT INFLAM.	SYSTEMIC MANIFEST.	MORNING STIFFNESS	JOINT PAIN	JOINT DEGENERATION	
								P.E.	X-RAY
12508–02	F	83					+	+ + + +	+ + + +
25408–02	F	52				+ + +	+ +	+ + +	+ + + +
36708–02	F	53			+	+ + +	+ +	+ + +	+ +
24512–02	F	62		+ +	+ +	+ + +	+	+ +	+ + +
23007–01	M	71	+ + +	+ + + +	+	+ +	+ + +	+ +	+ + +

In Table IV we again identify two familiar cases from Table I. We begin again with the typical case of degenerative changes with pain and nothing else; at the bottom can be seen the case that we agree was obviously mixed, and in between are three of the many possible intergradations. We believe that the question in the title of this chart is entirely proper. "What is degenerative joint disease?" We used to think we knew, but now we have seen so much "mixed" that we, ourselves, are mixed up and do not know where on this gradient to put the cut-off point. Should we permit morning stiffness as in the second case, fatigue as in the third case, inflammatory changes as in the fourth case? We are inclined to evade this problem, at present, by avoiding nosologic terms, and using instead such descriptive phrases as "a patient with degenerative changes and pain" or "one with degenerative changes, pain, and morning stiffness," etc.

We believe that morning stiffness and degeneration in joints are important variables. And, we ask the question, are they not the key manifestations of two entirely unrelated rheumatic processes?

We have shown why we need limiting definitions laterally between disease in Table IV and horizontally at the minimum severity at which the diagnosis is acceptable in Tables II and III.

Are there any statistical techniques to help us unravel these problems which heretofore have been solely the province of clinical judgment? The answer is unequivocally yes!

We can, in population studies such as are now in progress in Pittsburgh, actually calculate the prevalence rates for any set of symptoms and signs that occurs with reasonable frequency. Such prevalence rates, particularly if made specific by age, sex, or other variables, can materially assist the clinical judgment of experienced physicians when they set out to establish limiting definitions.

This problem concerned with definitions is not limited to the field of arthritis; it exists throughout all of medicine, for our textbook pictures of diseases are of the "usual case" or the "classical case," and the problem of drawing vertical dividing lines, i.e., differential diagnosis, is looked on as the most prized of the arts. Furthermore, the problem of the minimum severity at which a diagnosis is acceptable is only occasionally given attention. In the field of rheumatism, the criteria for rheumatic fever, set forth by the late T. Duckett Jones,* stand out as a model. Further attempts at precise definition of disease states should be hailed as advances even if only partially successful.

SUMMARY

The need for limiting definitions in the rheumatic disease field has been emphasized. Definitions must draw sharp lines between diseases and at the minimal severity at which a diagnosis is acceptable. This need is just as great for the clinician planning therapeutic trials as for the epidemiologist studying the distribution of disease in the population.

*Jones, T. D.: The Diagnosis of Rheumatic Fever, *J. A. M. A.* **126**:481, 1944.

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Reviews

MEDICAL MANAGEMENT OF CIRRHOSIS OF THE LIVER

CHARLES S. DAVIDSON, M.D.

BOSTON, MASS.

From the Thorndike Memorial Laboratory, Boston City Hospital

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CHRONIC liver disease may arise from or may be the result of a number of clinical situations; for example, chronic hepatitis occasionally follows the acute viral disease. A form of chronic hepatitis is sometimes observed in brucellosis, sarcoid, syphilis, and Wilson's disease. Hepatic functional impairment, together with pathologic changes, is associated with protein malnutrition in many parts of the world, especially in the tropics; and in a severe form in alcoholics, chiefly in the more temperate zones. This latter form has been longest recognized, most extensively studied, and forms the prototype for understanding the pathologic physiology and treatment of liver disease of other etiologies. The terminology is not easy, but for the purposes of the discussion to follow the term "cirrhosis of the liver" is employed to include cirrhosis in alcoholics, nutritional cirrhosis in nonalcoholics, and all other forms of cirrhosis, including the so-called healed acute yellow atrophy, toxic cirrhosis, biliary cirrhosis, and the cirrhosis which occurs in Wilson's disease. Most of the present discussion, however, is derived from experience with the chronic alcoholic with cirrhosis.

PHYSIOLOGIC BASIS OF TREATMENT

As with most other diseases, the medical management of cirrhosis depends to a considerable extent upon the wisdom, judgment, and experience of the physician, and has all too little present scientific basis. When given suitable opportunity, the liver exhibits a remarkable ability to repair damage. Specifically, under favorable conditions, one may expect (1) the disappearance of necrosis and of fatty infiltration and degeneration, and (2) regeneration of liver tissue, possibly with a decrease in fibrosis. Each of these will be discussed separately.

Diet and the Fatty Liver.—Experimental work in animals has led to the hypothesis that in man a protein-deficient diet leads to fatty infiltration and subsequent fibrosis, i.e., cirrhosis. Following the classic studies of Best and his colleagues,[1] Chaikoff, Connor, and Biskind,[2] György,[3] and Himsworth and

Glynn,[4] emphasis has been upon deficiency of protein and particularly of choline and methionine. The lipotropic action of these and other substances and the sequence of events in the development of experimental cirrhosis have been reviewed by Best and his colleagues.[5] Several matters must be considered, however, before the experimental data can be carried over to explain completely the cirrhosis of man. First, it is possible that alcohol may directly damage the liver, although Klatzkin, Gewin, and Krehl[6] suggested that alcohol increases the choline requirement. Second, it is not entirely clear that the acute alcoholic liver disease so frequently seen in man is the direct result of fatty infiltration. Indeed, patients have been observed to get rid of the excess hepatic fat without at the same time improving clinically; and in fact have died occasionally with little or no fatty deposits in the hepatic cells. In the latter group of patients there is some evidence that necrosis, Mallory bodies, and the parenchymal disorganization which appear in alcoholics with severe active liver disease are more often linked with the clinical illness and the subsequent development of fibrosis than is fat.[7] This lesion complex may be also a disturbance resulting from chronic protein undernutrition. Recently fatty liver disease and cirrhosis in the population (particularly infants and children) of many tropical countries of the world, generally lumped together under the term "Kwashiorkor," have received prominence.[8] Here again, there are some doubts that fatty infiltration of the liver alone necessarily leads to clinical evidence of liver disease or to subsequent fibrosis (cirrhosis). In spite of these problems, most students of the subject believe that chronic malnutrition, particularly of protein and also probably of choline and methionine, is one, perhaps the most, important factor in the genesis of these forms of active and chronic liver disease in man. Its prevention is believed to rest largely upon the consumption of an adequate diet, as well as upon avoidance of alcoholic beverages when they are implicated. The treatment of liver disease, when undernutrition has played a part in its genesis, is currently based upon the provision and consumption of good food, furnishing ample protein and members of the vitamin B complex. This concept was firmly established by the classic work of Patek and Post.[9]

Regeneration of Liver Tissue.—It is usually stated in textbooks that the liver has remarkable powers of regeneration. This certainly is true of experimental animals, in which removal of approximately 70 per cent of the liver is followed by regeneration to the original size within one week or so. It is not only remarkable that the liver regenerates so rapidly, but perhaps even more so that regeneration ceases when the liver has regained its normal size. The factors which control regeneration, both those which stimulate and depress it, are, however, little known. Animal experiments show that, at least for the normal liver, regeneration after hepatectomy requires a normal portal blood flow, the absence of biliary retention, and an adequate protein diet.[10] The relation to portal blood flow was shown long ago in the classic Eck-fistula experiments in which regeneration failed or was slow after blood had been diverted through the fistula and away from the liver. The reaction to biliary retention is not as clear, and is based upon some older experiments which may not apply to cirrhosis in

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man. There is little doubt that in the rat, as Vars and Gurd[11,12] have clearly shown, regeneration depends upon the protein content of the diet.

Regenerating nodules of liver tissue are almost invariable accompaniments of cirrhosis of the liver in man, as seen by biopsy or at autopsy. These nodules usually stand out in histologic sections as well as in the gross specimen. Whether they always contain functionally normal liver tissue and are from the first connected with the biliary tree have not been established, and there is some doubt that these cells are at once quite normal. Nevertheless, it is largely upon regeneration of liver tissue that permanent improvement in patients with chronic cirrhosis of the liver depends. There seems little doubt that fibrosis may be a factor limiting regeneration, although to what extent the liver is able to regenerate when fibrosis is present is not known. However, even in severely fibrotic livers seen at autopsy, many or even multiple regenerating nodules may be present. Although fibrosis may slow down or partially inhibit regeneration, it does not seem to prevent it altogether. Finally, it is possible that regenerating liver cells may "stretch" the fibrous tissue so that it appears less in amount and is functionally less important. These matters will bear further investigation.

Portal Hypertension.—The common complications of chronic hepatic disease most important as causes of death are ascites and edema formation, massive upper gastrointestinal hemorrhage, and hepatic coma. The first two of these are direct results of the portal hypertension which so commonly accompanies chronic hepatic disease. It is generally agreed today that portal hypertension depends upon obstruction to portal blood flow by the fibrosed liver, with an unknown, probably significant, and perhaps highly important contribution from intrahepatic arteriovenous connections (that is, hepatic artery–portal vein shunts).

There is little direct evidence (repeated measurements of portal pressure) to indicate that progressive reduction in portal pressure results in improvement from chronic liver disease. Considerable indirect evidence does exist, however. First, the decrease in the stuffing of liver cells with fat and the disappearance of necrosis with treatment would, one might expect, lead to more easy passage of blood through the liver and thus a decrease in portal hypertension. Second, liver cell regeneration might also lead eventually to a better portal vein circulation and the elimination of arteriovenous shunts. Third, the clinical evidences of portal hypertension, such as splenomegaly, ascites and edema, and visible collateral circulation on the abdominal wall, have been noted repeatedly to decrease or to disappear following sufficiently prolonged adequate therapy. Fig. 1 illustrates a patient in whom there was disappearance of ascites and edema, visible abdominal wall collaterals, splenomegaly, esophageal varices, and marked undernutrition when an adequate, but severely sodium-restricted, diet was continued for many months. These changes point to a reduction in the portal pressure and regeneration of liver tissue.

TREATMENT OF SPECIFIC MANIFESTATIONS OF CHRONIC LIVER DISEASE

Treatment of Undernutrition.—Chronic undernutrition, with wasting of both muscle mass and fat from the entire body, is one of the outstanding charac-

teristics of chronic hepatic disease. When such a patient has ascites and edema he resembles a spider with long spindly extremities and a paunchy abdomen (Fig. 1). The reasons for this chronic undernutrition are not wholly known. As with other nutritional disturbances, one should consider food intake, digestion and absorption, intermediary metabolism, and external losses of nutrients. Anorexia, particularly in alcoholics, is important, but not the entire cause. Treatment, therefore, must begin with the provision and consumption of an adequate diet sufficient in protein to allow positive nitrogen balance, and in calories to allow for proper utilization of other nutrients, and therefore for the building of body tissue.

There is little evidence for diminished digestion and absorption of nutrients in patients with chronic hepatic disease. Nitrogen balance studies indicate that the stool nitrogen is not increased above normal on a given protein intake.[13] No studies have been made of the total absorption of calories, but there is evidence of diminished fat absorption in some patients.[14] Whether this is sufficient to limit nutrition is doubtful and not definitely known.

Unquestionably, patients with liver disease have manifold abnormalities in intermediary metabolism. Just how far these defects, if present, limit nutrition is not known. It is known that under most circumstances it is possible maintain a positive nitrogen balance in patients with chronic, and even with acute, liver disease. However, the nitrogen balance is not always of the degree of positivity expected from the extent of undernutrition these patients show. This and the fact that, as improvement in liver disease occurs, an increasing positivity of nitrogen balance sometimes is seen have led to the concept that the defects in intermediary metabolism of protein in chronic liver disease limit the speed of regaining normal nutrition.[13] How limiting they are is not known except that, given an adequate diet over a long enough period of time, most patients with chronic hepatic disease, in whom the activity of the pathologic process has ceased, show gradual improvement in nutrition to normal. This is well illustrated by the patient in Fig. 1. Such a good result is not always the case, however, some patients dying of other complications of hepatic disease before sufficient time has elapsed to allow nutrition to improve. In other instances, little sign of improvement in nutrition is observed even though many months or a longer period has elapsed. The limiting factors in these latter cases are quite unknown, unless the regeneration of liver tissue is limited by fibrosis or in some other way.

Frequently an increased urinary excretion of amino acids is found in patients with chronic hepatic disease, but this is not limiting nutritionally.[13] An extremely depleting loss of nutrients occurs from repeated paracentesis. A paracentesis of 10 L. containing 2 Gm. of protein per 100 c.c. represents a loss of 200 Gm. of formed protein. Were this procedure necessary every ten days, the loss would be 20 Gm. of formed protein per day by this route, to say nothing of the losses of nitrogen in other forms and of other nutrients in the ascitic fluid, including sodium, potassium, and perhaps vitamins. The effective control of ascites formation by a sodium-restricted diet, discussed later, is extremely important in preventing these losses of nutrients from the body.

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A suitable diet for the treatment of undernutrition presumably would supply the nutrients necessary not only to provide improvement in the nutritional status, but also to repair the deficiencies which may have led to fatty infiltration, necrosis, and parenchymal disorganization of the hepatic cells. What this diet should contain has been a matter of considerable argument and discussion in recent years. Our own emphasis, following the pioneer work of Patek and Post[9] and of others, has been first that the foods must be consumed by the patient and, second, that they must be nutritious, well balanced, and supplying at least the optimum allowances of nutrients (as, for example, those specified by the National Research Council's Food and Nutrition Board[15]). Emphasis has been on high-quality protein; and in most instances, as patients do not always make a wise choice, on a somewhat higher than normal protein intake.

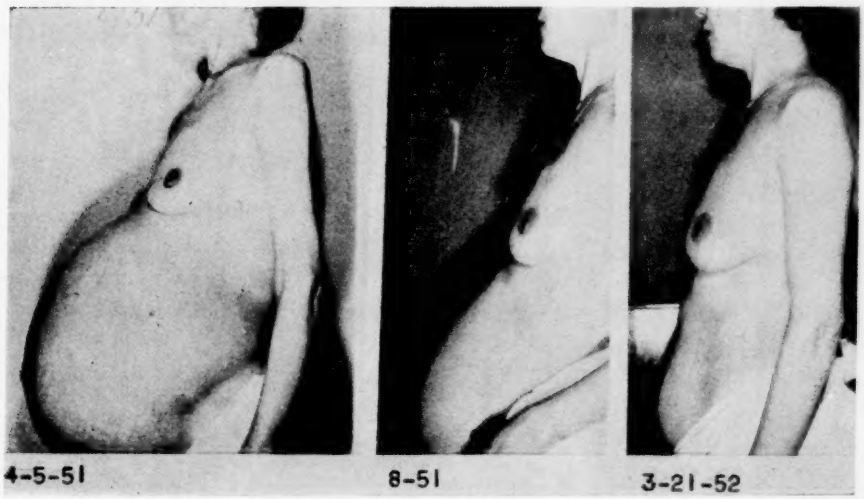

Fig. 1.

A diet supplying 2,000 to 2,500 calories per day, with between 70 and 100 Gm. of protein, much of it from animal sources, and having sufficient fat to make it palatable and attractive, is the basis from which we work. The foods comprising such a diet may be given in three meals a day, or may be better tolerated by many patients as more frequent smaller feedings. Emphasis has not been placed upon diet supplements such as commercial protein materials, upon multivitamin preparations, or upon additional choline or methionine in addition to that furnished in the diet except under special and unusual circumstances, such as either evidences of specific nutritional deficiency or the impossibility of feeding the patient sufficient good food to furnish these nutrients in reasonable quantities.

A diet commonly used on the Thorndike Ward for prolonged treatment of patients with chronic hepatic disease is shown in Table I. The estimated quantities of choline, of methionine, and of thiamine, riboflavin, niacin, and iron are included, as well as protein, carbohydrate, fat, and calories. According to the

TABLE I. STANDARD SODIUM-RESTRICTED DIET

WT. (GM.)	FOOD	PROTEIN* (GM.)	FAT* (GM.)	CARBO-HYDRATE* (GM.)	CALORIES*	SODIUM† (MG.)	THIA-MINE* (MG.)	RIBO-FLAVIN* (MG.)	NIACIN* (MG.)	METH-IONINE‡ (GM.)	CHOLINE CHLORIDE ‡ (MG.)
200	Grapefruit juice	1.0	0.1	9.8	76	2.0	0.03	0.02	0.20	——	——
50	Egg	6.4	5.8	0.4	81	65.0	0.04	0.14	0.05	0.3	865.0
30	Cream	0.9	6.0	1.3	61	18.3	0.01	0.04	0.03	0.03	4.4
125	Sodium-restricted bread	10.1	3.4	75.0	344	7.3	0.30	0.19	2.80	0.15	41.6
80	Sweet butter	0.4	64.8	0.3	572	8.0	——	——	0.08	——	10.4
100	Cabbage	1.4	0.2	5.3	24	15.0	0.03	0.03	0.20	——	251.0
200	Potato	4.0	0.2	38.2	166	6.0	1.80	0.06	2.00	0.1	212.0
60	Beef	11.7	6.6	——	109	42.0	0.05	1.00	2.80	0.3	40.8
30	Lamb	5.4	5.3	——	70	27.0	0.05	0.07	1.60	0.13	25.2
50	Asparagus	1.2	0.2	1.7	11	2.0	0.03	0.04	0.50	——	64.0
300	Peaches	1.2	0.3	54.6	204	6.0	0.03	0.06	2.10	——	——
100	Banana	1.2	0.2	23.0	88	1.0	0.04	0.05	0.70	——	——
120	Lonalac	32.4	33.6	45.6	614	18.0	0.40	1.68	0.84	0.12	17.6
180	Coffee	——	——	——	——	——	——	——	——	——	——
	Total	77.3	126.7	255.2	2,420	217.6	2.81	3.38	13.90	1.13	1,532.0

*Composition of Foods—Raw, Processed, Prepared: U. S. Department of Agriculture, Agriculture Handbook No. 8, Washington, D. C., June, 1950.
†Reference 16.
‡Values for methionine and choline chloride content of foods from:

1. Engel, R. W.: Choline Content of Animal and Plant Products, J. Nutrition **25**:441, 1943.
2. McIntire, J. M., Schweigert, B. S., and Elvehjem, C. A.: Choline and Pyridoxine Content of Meat, J. Nutrition **28**:219, 1944.
3. Lyman, C. M., et al.: The Methionine Content of Meat, J. Biol. Chem. **166**:173, 1946.
4. Block, R. J., and Bolling, D.: The Amino Acid Composition of Protein and Foods, ed. 2, Springfield, 1951, Charles C Thomas, Publisher.

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Food and Nutrition Board's recommended allowances, this diet is within the range for normal individuals. Whether the addition of more calories, more protein, or more vitamins would in fact increase the rate of recovery of these patients is doubtful, but not known. We have felt that until this was proved, the administration of more than this basic amount was unnecessary. In point of fact, however, most patients are satisfied with this quantity of food for relatively long periods of time, until they begin to show striking signs of improvement. At about this same time, appetite usually increases and the desire for more food sometimes becomes very great. When this occurs, enough is provided to satisfy the patient's desires. Again it should be emphasized that under no circumstances should the patient be allowed to eat less than an adequate diet, as here recommended, except when sodium requires restriction in the treatment of ascites formation, when protein requires restriction in hepatic coma (see later), or when all food must be eliminated because of massive gastrointestinal bleeding.

Treatment of Ascites and Edema.—Abdominal paracentesis is now seldom necessary for the relief of ascites and edema of patients with cirrhosis of the liver. The restriction of sodium intake to approximately 200 mg. daily will, in most instances, promptly halt further ascites formation. A few patients will require some restriction in fluid intake as well. Occasionally sodium restriction of this degree is followed promptly by progressive diuresis with complete loss of ascites and edema. More frequently, however, diuresis is delayed so that weeks, months, or even one year or more may be required before loss of ascites and edema is complete. The restriction of sodium intake to this low value is not difficult, but requires intelligent cooperation of the patient and attention on the part of the physician, nurse, and dietitian to every detail. The diet listed in Table I can be adapted easily to this degree of sodium restriction by eliminating salt and sodium compounds in preparation and cooking the foods, and by the use of bread made without added sodium, sweet butter, and most canned vegetables packed without added salt. Because meat and many other foods from animal sources are the most important source of sodium in the foods listed, the quantity of meat furnished daily must be limited somewhat to 3 ounces daily and one egg only is allowed. The principal source of protein, then, is a low-sodium milk product.* For some of the finer points with regard to the preparation of a sodium-restricted diet, the reader is referred to the National Research Council's Food and Nutrition Board Bulletin.[16]

It should be emphasized that only a few patients will have a prompt diuresis and loss of ascites and edema following rigid sodium restriction. In most instances all that can be expected is cessation of ascites formation within twenty-four to forty-eight hours after beginning the 200 mg. sodium diet. Great patience is then required with strict adherence to sodium restriction, sometimes for long periods of time, before the ascites leaves. The patient illustrated in Fig. 1 required approximately two years of rigid sodium restriction before the

*We have had good success with a low-sodium milk product, "Lonalac" (Mead Johnson & Company, Evansville, Indiana), which furnishes approximately 13 mg. of sodium per 100 Gm. of the powder. It is usually well taken but, if necessary, can be flavored for variety.

ascites disappeared. During the first few months she required moderate water restriction (1½ L. daily) as well. In her case, the disappearance of visible collateral circulation and the marked gain in body flesh are evident and began at about the same time as the ascites gradually disappeared. For this reason, diuresis was not accompanied by weight loss but rather by weight gain due to the gain in flesh. This phenomenon of ascites disappearance and gain in weight is to be expected in most but not all patients who adhere to sodium restriction for long periods of time. It is accompanied by an increased sense of well-being and strength, usually marked increase in appetite, and a return of libido and of axillary and often chest hair. It is probable that this change is due to regeneration of active liver substance. A progressive rise in serum albumin concentration and fall in Bromsulphalein retention is usual and gives additional evidence that liver-cell regeneration may be occurring.

Most patients with cirrhosis complicated by ascites and edema exhibit a moderate hyponatremia (130 to 135 meq. per liter). Occasionally the hyponatremia is more severe (120 to 130 meq. per liter). Under usual circumstances such hyponatremia is not a cause for alarm and does not contraindicate restriction of sodium intake. On the contrary, when diuresis occurs with strict sodium restriction, whether it be prompt or moderately or greatly delayed, hyponatremia, if present, gradually disappears and the serum sodium concentration returns to normal. When diuresis is prompt, there is usually a rapid return of the serum sodium concentration to normal due to an increased excretion of water above sodium in the early days of the diuresis.[17] When loss of ascites is a slower process, the rise in serum sodium concentration is likewise slow.

The pathogenesis of ascites is still a matter of considerable doubt and debate, although increased portal pressure and lowered serum colloid osmotic pressure (roughly proportional to serum albumin concentration) are the primary factors in cirrhosis of the liver. For further discussion of this matter, the reader is referred to recent work on the subject.[18,19]

Treatment of Massive Upper Gastrointestinal Hemorrhage, Particularly From Varices.—Massive upper gastrointestinal hemorrhage has been and still is one of the most frequent of the fatal complications of cirrhosis of the liver. The management of these patients must depend upon as accurate a diagnosis as possible of the source of the bleeding. Patients with chronic liver disease, especially alcoholics, bleed perhaps more often from peptic ulcer or gastritis than from ruptured esophageal varices. Before considering surgical therapy it is therefore necessary to establish the source of the bleeding.

The nature of the bleeding episode itself may be of considerable help, for patients who bleed from esophageal varices usually note that the blood simply wells up in their mouth in large quantities and less frequently is actually vomited or occurs after frequent retching and vomiting. However, bleeding from peptic ulcer, gastritis, or even the esophageal tears found in the Mallory-Weiss syndrome may be massive. It has been our custom to visualize the esophagus and lower stomach with thin barium as soon as the patient is well stabilized and to perform esophagoscopy, usually in the bed, even during active bleeding. When esophagoscopy reveals active bleeding from varices, the diagnosis can be con-

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sidered established. If active bleeding from varices is not seen, only a provisional diagnosis of bleeding from this source can be made on the basis of the character of the bleeding and the presence of varices from barium swallow or the visualization of nonbleeding varices by esophagoscopy. When bleeding from varices has been proved or is considered highly probable, an esophageal or gastric balloon may be used in an effort to compress the veins supplying the area of blood loss. This has been a satisfactory procedure in our hands in many cases, but is not without its dangers, and the balloon should not be left in place longer than is considered necessary. Physicians with experience in using the balloon differ greatly in the length of time they recommend it be left in place, from a few hours to many days.

The treatment of shock with repeated blood transfusions (sometimes requiring 10 or even 20 pints within twenty-four or forty-eight hours) is often necessary and lifesaving. The frequent determination of blood hematocrit values, the maintenance of proper fluid and electrolyte balance, and careful observation of pulse and blood pressure are, of course, necessary.

Once the diagnosis of bleeding from varices has been made, and the patient is in reasonably satisfactory condition, transesophageal ligation of the varices has been our procedure of choice. This can be only a temporary measure and it is then necessary to consider the advisability of attempting to reduce the portal pressure and (hopefully) to collapse the varices by some sort of portacaval anastomosis.

This and other surgical considerations are discussed by Blakemore in the companion piece to this paper. From an internist's point of view, two matters must be considered: First, it may be questioned whether satisfactory and prolonged medical therapy after the ligation of bleeding varices has been given a fair trial. Data on this point are inadequate for a comparison with the results of the shunt procedure. It may not yet be said positively that carefully managed medical therapy is unsatisfactory. As illustrated in Fig. 1, many of the evidences of the portal hypertension may disappear with prolonged medical treatment. Second, although portal hypertension may be rapidly relieved by a shunting procedure, the operation is still attended by a considerable mortality. Alcoholics with liver function and clinical state satisfactory enough to be considered for operation are not frequent; recurrent bleeding is not entirely eliminated; and the return to alcoholism is so frequent as considerably to reduce the long-term effectiveness of surgical procedures. That there may be a difference in mortality and response to operation between the cirrhosis of alcoholics and patients with "postnecrotic" cirrhosis is suggested by the wide differences of opinion as to the effectiveness of surgical treatment. Finally, a shunting procedure should not be used for relief of ascites, for as pointed out previously, this complication of chronic cirrhosis can be satisfactorily controlled by a diet severely restricted in sodium, a procedure not attended by an appreciable mortality.

Treatment of Hepatic Coma.—Hepatic coma is the commonest terminal episode in cirrhosis, 36 per cent of Ratnoff and Patek's[20] patients having died of this complication. It occurs in both the acute and active form of liver disease (as in alcoholics or in viral hepatitis) and in the chronic or stabilized

form of the disease. It is at least equally as common in nonjaundiced as in jaundiced patients. In stabilized cirrhosis, hepatic coma does not represent progressive liver failure, but is more likely due to an excessive load imposed on the organism with an inadequate amount of remaining liver tissue.

Coma may be precipitated by most analgesics, hypnotics, and sedatives, especially morphine and paraldehyde. Great caution must be exercised in the use of any of these agents, particularly the latter two, in severe liver disease. Ammonium-containing compounds, for example, ammonium chloride, may also precipitate hepatic coma and should be administered cautiously, if at all. In susceptible patients, protein in large or even moderate amounts may induce impending hepatic coma or deep coma. As protein is necessary for good nutrition and also presumably for healing of the damaged liver and regeneration of liver tissue, the physician is on the horns of a dilemma when evidence exists that protein feeding has been a factor in inducing hepatic coma. It is our custom, if this is the case, to reduce the protein intake to between 50 and 75 Gm. per day and, in some instances, when protein is clearly implicated, to eliminate it altogether. Following acute infection, major operative procedures, abdominal paracentesis, and gastrointestinal hemorrhage, hepatic coma occurs all too commonly. To avoid this complication, these should be avoided if possible and operative procedures undertaken only when absolutely necessary.

The diagnosis of hepatic coma may be considered probable in a patient with severe liver disease who develops coma, although other causes of coma, particularly subdural hematoma in alcoholics, must be considered in differential diagnosis. The presence of the so-called "flapping" tremor, fetor hepaticus, and the typical electroencephalogram strongly supports the diagnosis of hepaticoma.

Once the diagnosis has been established of either impending or deep hepatic coma, the physician must realize he is treating a condition with a high mortality rate, yet one which proper management may lead to recovery in a small number of patients. Management must be meticulous in every respect, much as in diabetic acidosis and coma.

General Care.—Patients with impending coma may be allowed to sit up or even to be out of bed, depending upon their state of confusion. If bed rest is necessary, frequent change in position and other measures to prevent hypostatic pneumonia, decubitus ulcers, and aspiration pneumonia are necessary. Sedatives should rarely, if ever, be administered, even when the patient is excited (as he frequently is, particularly at night). If considered necessary, small amounts of barbital or phenobarbital may be used for sedation. To control pain, Demerol is considered the best analgesic. These drugs are not without their dangers, however. Morphine, methedon, and paraldehyde should rarely be used and under no circumstances if evidences of impending hepatic coma are present.[19]

Feeding.—If the patient can eat, solid food should be given. If not, tube feeding should be used, preferably using a small plastic tube well lubricated during passage. Parenteral feeding may be used if vomiting and aspiration are feared, or if the patient has diarrhea not amenable to aluminum hydroxide or bismuth subcarbonate (paragoric should rarely be used because of its content

of opium alkaloids). Because of the possible harmful effects of too much protein it has been our custom to supply between 50 and 75 Gm. daily, whether given by mouth or by tube. This is usually sufficient to maintain nitrogen equilibrium or positive nitrogen balance if sufficient calories are administered at the same time. Protein should be of high quality. Sodium restriction (200 mg. daily) is indicated if ascites is a major problem. If the serum potassium concentration is low or falling, and there is a good urinary output, 2 to 3 Gm. of potassium chloride should be given daily. Sufficient calories should be given to maintain adequate nutrition; i.e., in the neighborhood of 2,000 daily unless the patient has fever or other evidences of increased requirement. Some patients with hepatic coma have diarrhea if too high fat content in the diet is provided, so that this may have to be reduced.

Although there is little or no evidence that hepatic coma is due to lack of vitamins or is influenced by the administration of vitamins, our custom has been to supply daily "therapeutic" quantities of the vitamins of the B complex.* If the blood prothrombin concentration is low, vitamin K may be given parenterally but need not be continued for more than a few days. A response is rarely observed in liver disease. When feeding is not by mouth or by tube, a multiple-vitamin preparation should be given parenterally. Fluid and electrolyte balance is of the utmost importance, particularly when deep coma has supervened. It is necessary to measure accurately the fluid intake and output, including in the latter estimated insensible loss and vomitus. To measure fluid balance, it is essential to know the quantity of fluid ingested as well as that lost and, as a check, body weight should be measured daily.

When the patient is in deep coma, we have fed by tube a mixture composed of 200 Gm. of Lonalac, 400 c.c. of 20 per cent cream, 200 Gm. of Dexin,† one teaspoon of Vi-magna Granules,* and water sufficient to meet the fluid requirements. This mixture furnishes about 65 Gm. of protein, 2,400 calories, 270 mg. of sodium, and 3.2 Gm. of potassium daily, as well as vitamins listed in the footnote. No more of this mixture nor of any other fluid should be given daily than is necessary to cover the daily losses, unless it is believed that the patient is dehydrated, in which case a trial of an additional 1 or 2 L. of fluids is called for, but then for no more than twenty-four or forty-eight hours. If no increase in urinary output is observed, a return to an intake equivalent to the output is necessary. Most patients with hepatic coma have oliguria, which is quite independent of dehydration. The continued administration of more fluid without sodium than is necessary results in progressive hyponatremia, which may contribute to the state of coma. This can be avoided by careful watch of the fluid balance and weight in each patient. A catheter must be used in all patients in whom urine collections are necessary and who are incontinent or otherwise unreliable in collections.

If severe hyponatremia is present, occasional individuals will respond with improvement in the state of consciousness to the administration of hypertonic

*We have added to our tube-feeding mixture, approximately 2 Gm. of Vi-magna Granules per quart (supplied through the kindness of Dr. Ruegsegger of Lederle Laboratories, Pearl River, New York). This supplies vitamin A 5,000 USP units, vitamin D 500 USP units, thiamine 3 mg., riboflavin 2 mg., vitamin B_{12} 1 μg, niacin 20 mg., ascorbic acid 75 mg., folic acid 1 mg., calcium pantothenate 1 mg., and pyridoxine 0.2 mg.

†Burroughs-Wellcome and Company.

saline solution. This, however, should not be used unless the hyponatremia is severe and there is good reason to believe that it contributes to the comatose state. Occasionally the serum potassium will fall to low levels, as mentioned previously, in which instance potassium should be given parenterally. Paracentesis should never be performed in patients with impending or deep hepatic coma unless there is severe respiratory embarrassment and then only small amounts of fluid should be removed at one time.

In addition, patients must be followed carefully clinically and by laboratory determinations, as follows: A record must be kept of the patient's mental and neurological status, the state of consciousness, and the presence of a "flapping" tremor.[21] Blood pressure sometimes is low in hepatic coma. A record should be kept, and, if necessary, noradrenalin may occasionally be used. A daily hematocrit and frequent white blood counts are necessary. The serum sodium, potassium, nonprotein nitrogen, and carbon dioxide-combining power should be measured frequently, sometimes daily, unless the patient's course remains unchanged for a considerable period of time in which case these determinations may be made at less frequent intervals. In jaundiced patients, measurement of the serum bilirubin or of the icterus index should be made at frequent intervals as a measure of the activity of the hepatic disease.

A few other specific therapeutic measures may be considered. Glucose in hypertonic solution has been advocated in the treatment of hepatic coma. Some patients may show a temporary response to its use. Certainly patients in deep coma, in whom caloric intake is difficult to achieve, should receive hypertonic glucose. Large intravenous infusions of normal human serum albumin are dangerous in patients with severe liver disease because of the possibility of inducing bleeding from esophageal varices or occasionally acute pulmonary edema. Nevertheless, small quantities of albumin may be given intravenously daily to patients with severe ascites and edema with the expectation that occasionally some diuresis will be achieved.

The intravenous administration of glutamic acid has resulted in lightening of the coma in occasional patients,[22] although the results have certainly not been uniform.[23] If available, it should be given as sodium glutamate intravenously, slowly, in a dose of 20 Gm. or more daily. Dramatic therapeutic benefits should be expected uncommonly. This amount of sodium glutamate furnishes large quantities of sodium which may increase the ascites and edema formation in patients with hepatic coma. The rationale for the use of glutamic acid depends upon its presumed ability to combine with ammonia to form glutamine, ammonia being considered one of the presumed "toxins" and resulting from failure of the liver to metabolize to urea the ammonia which is presumably produced in the gastrointestinal tract.

Occasional patients have appeared to respond, at least temporarily and occasionally perhaps permanently, to the administration of adrenocorticotrophic hormone (ACTH) or to cortisone, the latter in large doses. The use of these two drugs in hepatic coma has yet to be satisfactorily evaluated, and more study is necessary before it will be known how often therapeutic benefit is to be expected. Certainly both of these hormones can produce deleterious effects, especially in the presence of peptic ulcer or other forms of gastrointestinal bleeding, so that

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they should be used only when other therapeutic measures have failed and the situation seems desperate.

The antibiotics, tetracycline and particularly chlortetracycline, have been given to patients with hepatic coma. In some instances a lightening of the coma or return to normal state of consciousness has occurred. It is difficult to evaluate the action of these drugs, which are not without their dangers. Several patients have died of gastrointestinal bleeding following their use, and in a few instances a fatal acute staphylococcal diarrhea has occurred.

The treatment of hepatic coma must require expert judgment and meticulous care. Even under these circumstances, the complication is usually fatal. However, recently it has been possible, using the regimen outlined previously, to maintain, sometimes for many weeks or longer, patients with impending hepatic coma and occasional bouts of deep coma. It is possible that as we know more about the pathogenesis of hepatic coma, patients may be kept alive for considerably longer periods of time, an opportunity presented for liver regeneration to occur, and (hopefully) the whole process may then be reversed to recovery.

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OTHER THERAPEUTIC MEASURES FOR SPECIFIC FORMS OF LIVER DISEASE

Treatment of Specific Infections.—As active liver disease and cirrhosis may be caused by or follow certain specific infections including syphilis, brucellosis, schistosomiasis, and probably others, these should be treated by means appropriate to the infection concerned.

Alcoholism.—Most cases of cirrhosis of the liver in this country are associated with chronic alcoholism. As previously noted, it has not been finally established whether alcohol itself has a toxic action upon liver cells as well as a function in supplying calories at the expense of protein and other specific and essential nutrients. Whatever the circumstance may be, the treatment of alcoholism is necessary, if often discouraging, in the management of the patient with cirrhosis who recovers sufficiently again to become part of a social world. It is not the purpose of this paper to discuss the specific treatment of alcoholism by means of drugs or psychiatric therapy. Whatever adjuncts are used, the physician's attitude toward and interest in his patient are important, if not the most important, therapeutic measures. It is our custom to see these patients regularly and at as frequent intervals as possible after discharge from the hospital. They have learned that alcohol acts as a poison to them, that but one drink is enough to start the entire cycle going again, and that their livers are not now and presumably never will be able to withstand further bouts of alcoholism. This is discussed with them during therapy in the hospital, rather from the point of view of education than of inducing fear. Every effort is made to have the patient discuss his alcoholic problem freely with his physician. The prognosis is poor unless the patient admits freely to himself and his physician that he has been an alcoholic and that he has made up his mind to refrain from all forms of alcoholic beverages for the rest of his life. The patient is treated with kindness and consideration although with firmness and without mincing of words. He is not made to feel that his previous alcoholic habits were "bad"

or sinful, but rather that he had the misfortune to become addicted to a poison. Problems of a social or emotional nature are discussed with the patient as openly as possible, and the danger of holidays such as Christmas and New Year's, of a wedding, or of a wake are pointed out to him. He is encouraged to join Alcoholics Anonymous. The physician has failed in his duty if he does not take every means available to prevent the recurrence of alcoholism in a patient who has previously suffered from this disease. Under the most favorable circumstances, however, the relapse rate is still high.

Treatment of Pigment Cirrhosis.—Pigment cirrhosis (hemochromatosis) is a condition of unknown etiology in which there is marked cutaneous pigmentation, associated with diabetes and evidences of moderate or even severe liver disease. Occasional instances have been reported in which the disease is attributed to repeated blood transfusions over a prolonged period of time, as in aplastic anemia, or from the frequent administration of intravenous iron. However, in most instances it is an idiopathic disease, presumed to be due to an abnormally high absorption of iron from the gastrointestinal tract. In addition to the pigmentation, diabetes, and hepatic disease, there is usually a high serum iron and a saturated iron-binding capacity. Pathologically, the liver, usually the pancreas, and often many of the endocrine organs contain large quantities of iron-containing pigment and may show extensive damage and fibrosis. The general treatment of pigment cirrhosis is identical with that of cirrhosis of other kinds, as outlined previously. Specifically, however, the large quantities of iron in the body can be reduced by repeated phlebotomy.[24] This therapeutic measure may usually be expected to diminish pigmentation, to increase a sense of well-being, and in perhaps about one-third of the patients to improve the diabetes to the extent that insulin is no longer required.[25] Evidences of improvement in hepatic disease are less marked with this therapy but may be observed occasionally. It has been our custom to remove between 2 and 4 pints of blood per month, evaluating the patient carefully and particularly the hemoglobin and serum iron concentration once every month or two.

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SUMMARY

1. The physiologic basis for the treatment of cirrhosis of the liver depends upon the disappearance of necrosis and fatty infiltration and the appearance of liver-cell regeneration under favorable circumstances.

2. The undernutrition characteristic of severe liver disease will improve with the provision of an adequate diet. The improvement is often slow, however, and may be limited by defects in intermediary metabolism in these patients.

3. Ascites and edema accumulation can be controlled by furnishing a diet severely restricted in sodium content. Prompt diuresis can be expected for only a few patients following this regimen. Delayed loss of ascites and edema in most patients follows prolonged (one month to one or two years) adherence to this regimen.

4. The definitive treatment of massive gastrointestinal hemorrhage in cirrhosis depends first upon an accurate diagnosis of the source of the bleeding. When the bleeding is from ruptured esophageal varices, multiple blood transfusions are indicated. Balloon tamponade and transesophageal ligation of the

varices are often indicated to control and prevent recurrence of bleeding. Portacaval anastomosis usually will reduce portal hypertension. Whether it will be as satisfactory as optimal medical therapy remains to be proved.

5. Hepatic coma, the commonest terminal episode in cirrhosis, may be precipitated in susceptible patients by operative procedures, injudicious use of hypnotics and sedatives, the administration of ammonium salts, and a high-protein diet. Management depends upon expert and precise judgment, and attention to protein intake, fluid, and electrolyte balance, and under some circumstances certain specific measures.

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THE SURGICAL TREATMENT OF CIRRHOSIS OF THE LIVER

ARTHUR H. BLAKEMORE, M.D.

NEW YORK, N. Y.

From the Department of Surgery, Columbia University College of Physicians and Surgeons, and the Surgical Service of the Presbyterian Hospital

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WITH the development of successful portacaval shunting for the relief of portal stasis and portal hypertension, surgery has assumed a role of increasing importance in the treatment of cirrhosis of the liver. (The term "portacaval shunt" covers the use of the portal vein in direct anastomosis with the vena cava, or the employment of large portal radicles, such as the splenic vein, anastomosed to the left renal vein, familiarly called a "splenorenal shunt.") Portacaval shunting has proved to be an effective, rational, and relatively safe procedure, the main purposes of which are: (1) to protect patients from untimely death due to hemorrhage, and (2) to protect the liver from the deleterious effects of recurring hemorrhage and of wasting ascites.

The distorted pattern of hepatic architecture is the characteristic feature of cirrhosis. These changes, taking place during the natural history of Laennec's cirrhosis, inevitably result in obstruction to inflow of the portal blood.

Recently, Madden and his co-workers[1] reported a study of the intrahepatic circulation of livers from fresh cadavers by injections of colored solutions of neoprene latex. Yellow latex was injected into the portal vein, red in the hepatic artery, and blue in the hepatic (systemic) veins. Hydrochloric acid (30 per cent) was employed for corrosion of the liver parenchyma. In the study, whole specimens of the liver from twenty-three fresh cadavers were injected and corroded.

A study of the three specimens of normal liver revealed a uniform pattern of the intrahepatic circulation, with the tributaries of the portal and hepatic artery in constant equilibrium. There were no demonstrable intrahepatic communications between the hepatic artery and the portal vein, or between the hepatic artery and the hepatic veins. On the other hand, evidence of intrahepatic communications between the portal vein (yellow) and the hepatic veins (blue) was depicted by the appearance of a chartreuse color, which was interpreted as indicative of an admixture of the two primary colors—yellow (portal system) and blue (hepatic veins). This interpretation would appear to leave unclarified what route hepatic artery (red) blood takes to gain access to the outflow (hepatic vein) system.

In fourteen liver specimens the effects of cirrhosis on the pattern of the intrahepatic circulation were studied by these observers. In ten, irreversible ascites had been present clinically, and in four, ascites had been absent. The most significant feature of the study concerns the pathogenesis of ascites. In cirrhosis of the liver with irreversible ascites, Madden and his co-workers observed an absolute increase in both portal venous and hepatic arterial beds (the inflow tracts) and an absolute decrease in the hepatic venous bed (the outflow tract). Contrariwise, in cirrhotic livers from patients in whom ascites had been absent, the vascular pattern was characterized by a deficit in all three vascular systems, more pronounced in the portal and hepatic systems. These observations were confirmed in an extended study of the related histopathologic changes, as follows: (1) In cirrhosis of the liver with irreversible ascites there was a marked increase in the size of the portal vascular bed and a concomitant decrease in the number of the central or hepatic veins, the majority of which were occluded by obliterative fibrosis. (2) In cirrhosis of the liver without ascites, or with ascites of the acute or reversible type, there was a diminution in both the number and size of the portal and central veins.

These authors concluded from their studies on cirrhosis of the liver that irreversible (intractable) ascites results from obstructive fibrosis of the hepatic veins and is, therefore, an organic occlusion refractory to the generally accepted methods of treatment. Contrariwise, in acute, temporary, or reversible ascites, obstruction to the outflow tract (hepatic veins) is believed to be temporary, due primarily to cellular edema. Proper diet and medication in such patients result in subsidence of the intrahepatic cellular edema, and with improvement in the blood flow through the hepatic veins, the ascites disappears.

It is important knowledge that one can determine, on the basis of the character of the histopathologic changes in cirrhosis of the liver, the presence or absence of ascites as an associated clinical manifestation, and whether or not the ascites is intractable (irreversible). The diagnostic and prognostic value of the liver biopsy is greatly enhanced by the work of Madden and his associates.

In a discussion of ascites in terms of obstruction to the outflow tract (hepatic veins), one naturally considers the possible role of the hepatic lymphatics in decompressing an engorged liver. The experiments of Nix, Mann, Bollman, Grindlay, and Flock[2] revealed that in dogs with experimentally produced hepatovenous congestion, and in dogs with ascites due to experimental cirrhosis, the flow of hepatic lymph was two to five times that in normal dogs, and the protein content of lymph was increased 200 to 400 per cent. Our present concept of the intrahepatic circulation in the human liver is consistent with an increased flow of hepatic lymph in the presence of obstruction to the outflow tract (hepatic veins). There are two inflow tracts (hepatic artery and portal vein) delivering blood to a large capillary system (sinusoids) from which there is but one outflow tract, the hepatic veins. The sinusoids, in their course through the liver parenchyma, are in close proximity to liver cells and a network of intrahepatic lymph channels. It is logical to expect that obstruction in the outflow tract (hepatic veins), resulting in stasis of blood in the sinusoids, would effect alteration in diffusion pressures favoring an increase in hepatic lymph flow. As

evidence of this, we have repeatedly observed at operation many greatly distended hepatic lymph channels within the hepatoduodenal ligament.

By direct measurements of the portal pressure at the operating table, surgeons have confirmed the association of portal hypertension with obstruction to the inflow of portal blood in patients having cirrhosis of the liver. It has been our practice, in taking portal pressures, to record readings from a distal tributary of the portal vein (right gastroepiploic vein) before and after temporary occlusion of the portal vein itself. The initial portal pressure recording (before occluding the portal vein) is interpreted in terms of the grade of portal hypertension (250 to 600 mm. saline solution) to indicate the degree of obstruction to the inflow of portal blood caused by the cirrhosis. The final portal pressure (following occlusion of the portal vein) may be interpreted as giving an indication of how much portal blood is by-passing the liver via collateral venous channels, or the efficiency of this by-pass in a given case. Our experience has been that there is no rise, or but slight rise, in the portal pressure following compressive occlusion of the portal vein in the majority of patients having cirrhosis of the liver who come to operation; in some patients the portal pressure may rise 100 mm. (saline solution), but in few is this figure exceeded. In striking comparison, compressive occlusion of the portal vein in patients having no obstruction to portal blood flow results in a sudden rise of portal pressure from the average normal range (100 mm. saline solution) to 500 to 600 mm. (saline solution). This behavior in the normal subject suggests inadequacy of by-pass venous channels to meet the immediate demands of sudden portal vein occlusion.

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THE ROLE OF COLLATERAL AND BY-PASS VENOUS CHANNELS IN PORTAL BLOCK

The time-honored concept of the development of certain collateral channels, for example, between tributaries of the coronary and esophageal systems of veins in response to a rising portal pressure, as the result of progressive portal block is well known to all. High resistance to blood flow through the coronary-esophageal collateral circuit results in pressure dilatation of exposed mucosal veins predisposing to their rupture. Palmer[3] gave some idea of the magnitude of intraluminal strain as a factor disposing to rupture of varices by the determination of venous pressure within esophageal varices. Concomitant needle puncture readings from an esophageal varix and a portal radicle have been demonstrated to be of the same magnitude. In the course of operation on the portal venous bed, there have been many opportunities for measuring directly the portal venous pressure. These measurements have indicated clearly the close relationship between portal venous hypertension and the pressure within varices.

A wide range in portal venous pressure readings (250 to 600 mm. saline solution) has been recorded by us at operation in patients having esophageal varices secondary to cirrhosis of the liver. The lowest portal venous pressure reading in a patient giving a history of gastrointestinal bleeding was 270 mm. (saline solution). The persistence of portal hypertension in patients having esophageal varices secondary to cirrhosis of the liver may be taken as evidence

of inadequacy of and high resistance to blood flow of the portal collateral anastomotic circuits.

PORTAL STASIS—AN INDEX OF PORTAL COLLATERAL INEFFICIENCY

Hunt[4] has recently presented convincing studies demonstrating portal stasis in portal collateral circuits in association with portal hypertension. The flow through collateral anastomotic channels was estimated as follows: Phlebograms were taken at operation employing accurately time-spaced twin exposures. Comparison of the relative densities of the opacifying media in the two phlebograms, related to the time elapsed between exposures, affords an index of speed of blood flow through collateral anastomotic channels. Hunt concluded from the twin phlebogram study of natural collateral anastomotic channels that the blood flow through these channels was extremely sluggish.

Hunt measured the speed of blood flow in the portal vein as follows: A small quantity of radioactive sodium is injected into a radicle of the portal vein distally, and the speed with which the head of the injection traverses a given length of the portal vein is observed. The passage of the radioactive sodium along the portal vein was recorded by a double probe scintillation detector electronically coupled with a pen recorder. Speed of blood flow was measured in normal subjects and in patients having cirrhosis of the liver. Hunt observed that speed of blood flow in the portal vein of normal subjects averaged 10 cm. per second. In patients having cirrhosis of the liver the average speed of portal blood flow was slightly over 4 cm. per second, and in advanced cases a speed of little more than 3 cm. per second was noted. Hunt's findings indicate that collateral venous channels do not ensure normal blood flow velocity in the portal system in the presence of portal block.

Evidence has accumulated that casts doubt upon the likelihood that the development of multiple anastomotic collateral venous channels offers the only route for decompressing the portal system in the presence of portal block. Recently, Madden and Lore,[1] employing colored solutions of neoprene latex for injecting the caval and portal systems of veins, have demonstrated the presence of performed portacaval shunts in four of eight unselected human specimens. The presence of performed portacaval shunts would best explain why many patients who have cirrhosis do not develop esophageal varices and account for survival of patients in those well-documented cases of ligation of a fully patent portal vein.

PORTACAVAL SHUNTING

A portacaval shunt between the portal vein and the vena cava, or between a large tributary (splenic vein) and the left renal vein, is a logical and rational procedure for the relief of portal hypertension and the correction of portal stasis. These types of portacaval shunts are large channels offering a low resistance to blood flow. They are capable of shifting a large volume of blood rapidly from the high-pressure (portal system) to the low-pressure (caval) system of veins and, in so doing, effect a reduction in portal pressure with a relief of portal stasis.

Hunt studied the effects of portacaval shunting on portal stasis in patients with cirrhosis by measuring the speed of portal blood flow before and after the establishment of shunts, with results as follows: The speed of portal blood flow averaged 4.6 cm. per second in five patients before shunting. After the establishment of end-to-side portal vein–to–vena cava anastomoses, the speed of blood in the portal vein increased to average 12 cm. per second, or 2 cm. per second higher than the average normal of 10 cm. per second. An average speed of 7.2 cm. per second was noted to follow the establishment of splenorenal shunts.

A few surgeons early appreciated the potential usefulness of portacaval shunting for the relief of portal hypertension and portal stasis. Vidal,[5] in 1903, was the first to report a successful shunting operation. During the ensuing decade a few reports of cases appeared in the literature, essentially of single cases, notably by DeMartel[6] and Rosenstein.[7]

Believing that advances in preoperative preparation, anesthesia, the prevention of shock, and the control of infection would have an important bearing on the clinical success of portacaval shunts, Whipple and I undertook a restudy of the subject in 1943. The study now embraces a total of 262 shunted patients. The cases are divided into two groups, in accordance with the site of portal block; namely, extrahepatic (59 cases) and intrahepatic, due to cirrhosis (203 cases). In patients who have portal hypertension due to extrahepatic portal block, the site of block is in the portal vein, itself, thus rendering it unfit for shunting purposes. The splenic vein, therefore, must be preserved for shunting and not sacrificed by ill-advised splenectomy. The availability of a vein of adequate size for shunting is important to these patients who, unlike those affected with cirrhosis, have a normal life expectancy, once successful shunting is accomplished.

It has been documented again and again that splenectomy does not relieve portal hypertension or prevent the recurrence of gastrointestinal hemorrhage. For example, in the series of 59 cases, 25 patients (42 per cent) had had their spleens removed at a previous operation, without effect upon their tendency to subsequent attacks of gastrointestinal hemorrhage. Attempts at salvage in the 25 postsplenectomy bleeders (employing portal radicles for shunting of smaller size than the splenic vein) resulted in complete success in 36 per cent, partial success in 16 per cent, and failure to prevent the recurrence of severe attacks of gastrointestinal hemorrhage in 48 per cent. This compared to a salvage rate of 85 per cent in patients who had their spleens intact; and in whom, following splenectomy, the splenic vein was anastomosed end to side to the left renal vein. Experience has shown that the failure rate of splenorenal shunts may be further reduced if operation can be deferred in children until they reach 6, or preferably 8, years of age.

It is technically difficult to establish shunts in patients with extrahepatic portal block in whom the spleen has been removed at a previous operation; and, as stated before, the chances of getting a successful shunt are uncertain. On the other hand, esophagogastrectomy is not advocated in such patients, except as a last resort. We prefer first to conduct a careful search for a vein of suitable size for shunting; for example, a large portal collateral vein that can be an-

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astomosed to the vena cava (7 successful cases in our series). There is the possibility of doing the same with a superior mesenteric vein of suitable dimensions. In the absence of adequate veins, esophagotomy and suture of the varices may be performed forthwith. Unfortunately, in this group, procedures other than shunting also have an undesirably high incidence of failure: all of which again points to the fact that surgeons must not perform splenectomy on patients having portal hypertension due to extrahepatic portal block, unless they are prepared at the time to proceed with a splenorenal shunt, which, if properly done, offers the patient his best chance of cure.

The operative risk in portacaval shunting depends, other things being equal, on the normalcy of the liver. The liver was normal in 59 patients operated upon in whom the site of portal block was extrahepatic, and there were 4 postoperative deaths (6.7 per cent). In the 25 patients in whom the spleen had been removed at a previous operation, the mortality rate was 2.2 per cent higher than in patients with spleens intact. In contrast, the risk of shunting mounts rapidly in patients with badly damaged livers. For example, in the group of 203 patients with portal hypertension, the result of intrahepatic portal block due to cirrhosis, the over-all postoperative mortality was 19 per cent.

Children tolerate portacaval shunting well. In the series of 40 shunted patients, ranging from 2 to 15 years of age, there were no postoperative deaths. There were 2 follow-up deaths (not due to the disease) in 12 patients with cirrhosis, and 2 follow-up deaths (due to hemorrhage) in 28 patients with extrahepatic block.

We were aware, at the initiation of the study, of the potential risk of portacaval shunting in patients having cirrhosis of the liver. The commonly used biochemical tests of liver function were available to us, but unfortunately we had little experience interpreting their values in terms of risk for operations of this magnitude. Patients with Laennec's cirrhosis we knew best and were familiar with the importance of a careful history and physical examination in their clinical evaluation. For example, the outlook is poor in alcoholics of the older age group who give a long history of anorexia, weakness, and unremitting jaundice, and who exhibit jaundice, tissue wasting, a contracted small liver, and ascites. Characteristic changes in tests of liver function for such cases were as follows: Prothrombin time in excess of 4.7 seconds above normal*; cephalin flocculation 3 to 4 plus; serum bilirubin in excess of 1.5 mg. per cent; serum albumin values of less than 3.4 Gm. per cent; and Bromsulphalein retention in excess of 34 per cent one-half hour after injection. It should be stated that this range of values does not necessarily have the same grave meaning in patients having Laennec's cirrhosis of short duration, in whom the liver is of normal size or enlarged, and the same may be said for posthepatitic and other types of cirrhosis.

We did not often make the mistake of operating upon patients who, in the end stage of their disease, had at best an estimated life expectancy of but a few months. We did, however, accept for the shunting operation a great many

*Link and Shapiro method, plasma undiluted.

poor-risk patients, who exhibited a distinct tendency to recurring hemorrhage. The policy has subsequently seemed justified on the basis of studies which indicate but a 20 (Snell[8]) to 50 (Patek[9]) per cent chance of survival for medically managed patients one year after their first hemorrhage. The early adoption of this surgical philosophy, embracing a broad basis of acceptance for shunting to include poor-risk patients, would tend over the years to offset any percentage-wise reduction in operative mortality attributable to improvement in surgical management. On the other hand, it did not deny surgical therapy to those in whom it would appear to be the only chance of survival.

Our policy in accepting good-and poor-risk patients for the shunting operation resulted in the gradual accumulation of two substantial groups: Group "A," good-risk patients, and Group "B," poor-risk patients, classified in accordance with clinical evaluation, based primarily on liver tests. Table I shows the number and relative proportion of the two groups in our first sizable series of 117 shunted patients. Table II shows the averages of the preoperative liver function tests in Group "A" (64) and Group "B" (53) patients. The relative incidence of ascites in the two groups is also portrayed. Table III shows the preoperative liver tests of patients who died postoperatively, those who died subsequent to discharge from the hospital, and those still being followed.

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TABLE I. POSTOPERATIVE MORTALITY RATE IN 117 PATIENTS WITH INTRAHEPATIC BLOCK* DIVIDED INTO TWO GROUPS ACCORDING TO CLINICAL EVALUATION (A, GOOD RISK, AND B, POOR RISK)

	GROUP A		GROUP B	
	NO.	PER CENT	NO.	PER CENT
Total patients	64	55	53	45
Postoperative deaths	6	9.4	21	39.6

*Due to cirrhosis of the liver of Laennec's, posthepatitic, toxic, and obstructive biliary types.

Review of these tests provides criteria that may be helpful in evaluating operative risk and prognosis in a given patient, provided they are interpreted with special reference to the underlying disease process (see Table IV). For example:

1. Deep jaundice, as evidenced by a high serum bilirubin level, did not affect operative risk adversely in cases of cirrhosis secondary to common duct obstruction or hepatitis to the same extent that it affected adversely cases of Laennec's cirrhosis (see Tables III and IV).

2. High elevations of serum phosphatase in cases of posthepatitic or biliary cirrhosis would not seem to have affected operative risk unfavorably because all patients presented in Table IV survived. The serum phosphatase levels in Laennec's cirrhosis rarely exceeded 10 Bodansky units, and the highest value was 20.

TABLE II. AVERAGES LIVER TESTS IN PATIENTS WITH INTRAHEPATIC BLOCK SPLIT INTO TWO GROUPS (A, GOOD RISK, AND B, POOR RISK) ACCORDING TO CLINICAL EVALUATION

	GROUP A (64 PATIENTS)	GROUP B (53 PATIENTS)
Serum albumin (Gm. per cent)	4.2	3.4
Ascites F*	5	26
R†	2	6
None	57	21
Prothrombin time above normal (sec.)	3.3	4.7
Cephalin flocculation 3+ – 4+	19	23
1+ – 2+	42‡	30
Bromsulphalein retention after 30 minutes (per cent)	21.1	33.9
Serum bilirubin (mg. per cent)	0.87	1.5

*F = Failed to respond to medical treatment.
†R = Responded to medical treatment.
‡Cephalin flocculation test not performed in 3 patients.

TABLE III. MEAN VALUES FOR CERTAIN HEPATIC FUNCTION TESTS IN: (1) PATIENTS WHO DIED POSTOPERATIVELY, (2) PATIENTS WHO DIED MONTHS AFTER OPERATION, (3) PATIENTS WHO HAVE SURVIVED OPERATION

	NO. OF CASES	PROTHROMBIN, TIME ABOVE NORMAL (SEC.)	SERUM ALBUMIN (GM. PER CENT)	BROMSULPHALEIN RETENTION AFTER 30 MIN. (PER CENT)	SERUM BILIRUBIN (MG. PER CENT)
Postoperative deaths	27	5.5	3.58	30.3	1.38
Follow-up deaths	16	4.1	3.69	28.7	1.17
Alive	74	3.6	4.04	25.8	1.10

3. The impression has been gained that a strongly positive (3 plus to 4 plus) cephalin flocculation test more seriously affected operative risk in Laennec's cirrhosis than in posthepatitic cirrhosis.

4. Bromsulphalein retention of a given value affected operative outcome less in posthepatitic cirrhosis than in Laennec's cirrhosis (see Tables III and IV).

Analysis of the liver studies presented in Tables II, III, and IV provides a basis for better evaluation of operative risk in cirrhosis cases. More detailed analysis follows:

1. In patients with low preoperative values of serum albumin (less than 3 Gm. per cent in 16 patients), the postoperative mortality was 37.5 per cent and the follow-up mortality was 33.3 per cent.

TABLE IV. HEPATIC FUNCTION TESTS IN NINE SAMPLE PATIENTS DOCUMENTED AS TO TYPE OF CIRRHOSIS

NO. OF PT.	UNIT NO.	AGE	SEX	TYPE OF CIRRHOSIS		CHOLESTEROL		PERCENTAGE BROMSULPHALEIN RETENTION 30 MIN. AFTER INJECTION	CEPH. FLOC.	THYMOL TURBIDITY	SERUM ALK. PHOSPH. (B. U.)	SERUM PROTEIN		SERUM BILIRUBIN IMMEDIATE DIRECT (MG. %)
				POST-HEPATITIS	BILIARY (COMMON DUCT OBST.)	TOTAL (MG. %)	ESTER (MG. %)					ALB. (GM. %)	GLOB. (GM. %)	
1	977618	32	M	X		143		51	+++	+++	2.5	4	3.5	1.2
2	158982	41	M	X		326		44	++++	++++	11.6	4.1	3.3	7
3	111683	49	F	X				38	+++	+++	14	3.3	3	1
4	963397	31	M	X		201	133	49	++	++	20	4.1	2.2	1.2
5	142794	36	F	X		282	68	42	+++	+++	37	4.2	3.2	8.3
6	067543	37	F	X		347	234	23			46	4.1	4.7	2.8
7	143477	44	F	X		372	66	38			61	3.2	4.2	3.3
8	867336	41	F		X	235			Neg.	Neg.	22	3.4	4.6	6.8
9	712454	61	F		X	341	216	31	Neg.	Neg.	44	3.4	1.5	3.5

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2. In 51 patients in whom the prothrombin time was in excess of 4 seconds above normal, the postoperative mortality rate was 25.5 per cent.

3. In 44 patients in whom the cephalin flocculation test was 3 plus to 4 plus, the postoperative mortality was 29.5 per cent, and the follow-up mortality rate was 22.5 per cent, compared with 104 patients in whom the cephalin flocculation test was 1 plus to 2 plus, who had a 16.3 per cent postoperative mortality rate and 11.4 per cent follow-up mortality.

4. In 65 patients having a Bromsulphalein retention in excess of 20 per cent one-half hour after injection, the postoperative mortality was 27.7 per cent, compared to 73 patients in whom the postoperative mortality was 12.3 per cent when the Bromsulphalein retention was less than 20 per cent.

Sufficient data have been presented to indicate the value of carefully performed liver function studies as a guide to the evaluation of operative risk in patients having portal hypertension secondary to cirrhosis of the liver.

At the outset of our study, the known high incidence of liver failure associated with hemorrhage in patients having cirrhosis of the liver was sufficient warning against attempting to employ the shunting operation as an emergency procedure. Depending, as we were at the time, primarily upon transfusions for the treatment of bleeding esophageal varices, the patient who had frequent and prolonged attacks of bleeding posed a real problem in preoperative preparation for shunting. The result was evident, from analysis of our first substantial series of cases, that many of the postoperative deaths were in great part attributable to inadequate preparation of the patient, primarily in respect to time for recovery of the liver from the effects of hemorrhage.

In evolving a plan for the emergency management of patients with cirrhosis who are bleeding from varices, one must keep in mind that special pathologic factors are present, not ordinarily encountered when dealing with gastrointestinal hemorrhage due to other causes. There is the factor of increased portal venous pressure in portal hypertension. This, in itself, may contribute to persistent bleeding by interfering with the formation or adherence of thrombus at the site of rupture of a varix. A dyscrasia in blood clotting is frequently present or may quickly develop with the onset of hemorrhage in patients having severe impairment of liver function. The presence of such factors calls for the prompt institution of positive measures for the arrest of hemorrhage at the bleeding site.

There is no present method superior to the transfusion of whole blood for the treatment of shock resulting from blood loss. Unfortunately, experience has shown that dependence primarily upon transfusions in the emergency management of bleeding varices is not enough; other measures are necessary as follows:

1. Treatment of Shock
   - A. Transfusion of whole blood (if delayed, employ plasma, human albumin, or one of the plasma expanders).
   - B. Oxygen and other supportive measures.

2. Positive Measures for the Arrest of Hemorrhage at the Bleeding Site
   A. Esophagoscopy, packing with absorbable gauze or other hemostatic material.
   B. Esophagotomy, suture of the varices.
   C. Balloon tamponage.

There are few conditions more alarming to a patient than hematemesis. Therefore, the doctor may be reasonably assured of the willingness of his patient to cooperate in carrying out appropriate methods for the arrest of hemorrhage at the bleeding site. Livers affected with cirrhosis withstand anoxia, the result of diminished circulating blood volume, poorly. A survey of experience with transfusions alone, in the treatment of this form of hematemesis, indicates that many patients are spared death from shock only to succumb subsequently from liver failure.

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The proposal to incorporate, in a plan for emergency management, positive measures for the arrest of hemorrhage at the bleeding site brings us to the crossroad of decision. Shall we initiate, for example, balloon tamponage when the first transfusion is begun? Or shall we delay only until we are on the threshold of disaster? Our own experience indicates clearly that anoxia due to lowered circulating blood volume as the result of continued bleeding, transfusions notwithstanding, may severely damage a liver affected by cirrhosis in a matter of a few hours. In reviewing the records of a number of patients treated with esophageal balloon tamponage, an outstanding feature was the high incidence of liver failure and death associated with delay in treatment. For example, the recovery rate was 50 per cent higher in patients who had balloon tamponage started at the time of transfusions. Unfortunately, some delay in treatment is incurred in those patients who start bleeding outside of the hospital. However, even in outpatients there have been instances in which the nasogastric tube-bearing balloons have been passed, and hemorrhage successfully controlled before the patient started for the hospital. After all, it is as easy to pass the tube as it is to start a transfusion, and far quicker when there is the necessity of waiting for blood grouping and cross-matching.

Experience having indicated clearly that the maximum salvage of patients with cirrhosis complicated by hemorrhage hinges upon the prompt arrest of hemorrhage at the bleeding site, a short discussion of methods is in order. Esophageal and balloon tamponage have the important advantage of immediate availability for emergency use. Severe bleeding from a ruptured esophageal varix can be controlled by packing absorbable gauze into the esophagus via an esophagoscope. However, balloon tamponage, using a properly designed esophageal balloon and a stomach balloon mounted on a nasogastric tube, has proved to be a more efficient method for the arrest of hemorrhage.[10] The tube is well tolerated by the average patient (small doses of meperidine are required in some), and is ideally suited to the emergency management of patients having bleeding from varices, whether they be adults or children. Fig. 1 shows a photograph of a child-sized tube. Note the special feature of increased wall thickness of the lower portion of the esophageal balloon. This serves effectively to prevent

ballooning of the lower end into the stomach and maintains equal pressure upon varices up and down the esophagus. For control of bleeding in the occasional patient who has rupture of a varix on the stomach wall, the stomach balloon may be distended with the injection of 200 to 300 c.c. of air. Traction upon the tube then serves to compress the bleeding site by the balloon. Ordinarily the stomach balloon is inflated with 100 c.c. of air, which serves properly to position the esophageal balloon and prevent ejection of the tube, should emesis occur. Analysis of cases in which the institution of balloon tamponage has been followed by persistent bleeding commonly revealed that tamponage had not been started sufficiently early in a given case.

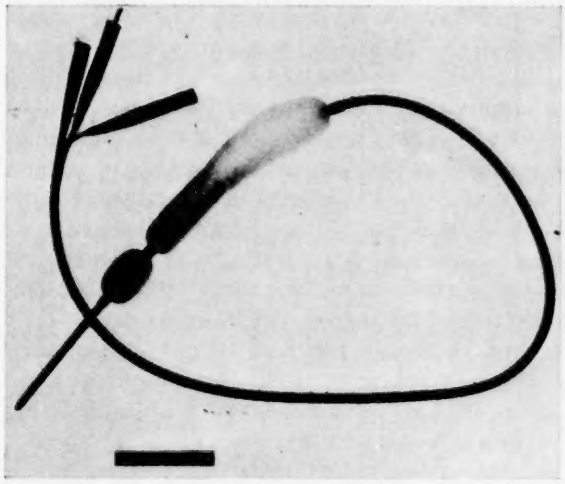

Fig. 1.—A photograph of a nasogastric tube with stomach and esophageal balloons inflated slightly. Note the reinforced portion of the esophageal balloon and the relatively large tube compartment for gastric aspiration.

It is well known that patients in irreversible shock or severe liver failure may bleed from a mucous membrane at any site. It is not reasonable under such circumstances, with a breakdown in the mechanism of blood clotting, to expect a total cessation of seepage of blood from the site of a ruptured varix gently compressed beneath a rubber balloon. The sudden onset of bleeding from multiple points on a dry wound surface coincident with the onset of shock is a phenomenon well known to the operating surgeon. The problem of failure due to delay is certainly a correctible one.

All hospitals should be equipped with an emergency tray containing a nasogastic balloon tube and accessories for its use.

One must not assume that with balloon tamponage established, the major work is past. The shepherding of a patient through a severe hemorrhage, who is subject to liver failure because of damage from cirrhosis, demands watchfulness and constancy.

Certain points of technique in employing the nasogastric balloon tube are

deserving of emphasis. Following the passage of the tube to the 50 cm. mark, 100 c.c. of air is quickly introduced into the stomach balloon to prevent ejection of the tube by emesis. Next, the tube is withdrawn sufficiently to bring the stomach balloon in gentle contact with the diaphragm. The tube is held in this position by a sponge-rubber ring about the tube which rests against the nose. The sponge rubber is held securely by adhesive fixing it to the tube. With this method of fixation no adhesive contacts the skin and the thick sponge rubber prevents damage to the nose, thus promoting comfort for the patient. At this point the esophageal balloon is inflated to a level not to exceed 45 mm. of mercury, and the tube is again checked to determine if the stomach balloon is, as it should be, in gentle contact with the diaphragm. Next, the stomach is emptied of blood clots as rapidly as possible employing a 50 c.c. syringe with a wide tip to aspirate and irrigate the tube. Only when the stomach is entirely free of old blood can one be sure of the complete arrest of bleeding. Therefore, it is essential that gastric samples be taken at hourly intervals, and their character recorded for at least twelve hours or until such a time when repeated blood-free samples would indicate safety in aspirating at two-hour intervals. It is most important that the doctor check the level of the diaphragm in relation to the stomach balloon shortly (one-half to one hour) after passage of the tube. At the time of passage of the tube, the muscles of the diaphragm go into spasm. Subsequently, with the relaxation of the muscles, the diaphragm will rise in the average patient 2 to 5 cm. and in some patients even more. This change in the level of the diaphragm necessitates withdrawal of the nasogastric tube until the stomach balloon is again just snug to the diaphragm. Since the degree of spasm varies from patient to patient, a third or a fourth adjustment of the tube in the first few hours of tamponage may be necessary.

If, upon emptying the stomach of old blood and adjusting the stomach balloon to the rising level of the diaphragm with relaxation of muscle spasm, there is no telltale evidence of bleeding in freshly aspirated gastric contents, a program for lowering the pressure in the esophageal balloon may be initiated. The first drop is adjusted to 35 to 40 mm. of mercury, and if aspirations are clear after two to three hours, the pressure may be further lowered to 30 to 35 mm. of mercury. A pressure at this level is tolerated well by the average patient, but a pressure level of 25 to 30 mm. of mercury is adequate for the control of hemorrhage in many patients. The esophageal balloon pressure should be maintained at that level which prevents bleeding in a given case for seventy-two hours, and should remain in situ but deflated for an additional twenty-four hours before removal.

MANAGEMENT OF THE REFRACTORY CASE

Unfortunately, one does encounter refractory cases, e.g., patients in whom a few hours or days following cessation of balloon tamponage there is recurrence of bleeding. It has been emphasized previously that a delay in the initiation of balloon tamponage greatly increases the problem.

It is the practice of some surgeons to test early for recurrence of hemorrhage by deflating the balloon at say twenty-four or forty-eight hours after the naso-

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gastric tube is passed and, if bleeding recurs, to suture the varices forthwith. Suturing esophageal varices requires a thoracotomy and an esophagotomy. It is, therefore, an operation of some magnitude. Furthermore, experience has shown that the procedure carries a considerable risk when performed upon patients whose livers are failing. Inescapable difficulties arise from a policy of routinely suturing varices in all patients who rebleed upon release of balloon pressure at a stated interval (twenty-four or forty-eight hours) after balloon tamponage is initiated. A routine attempt to suture varices during this period results in an excessive mortality rate, because the majority of such patients have a coagulation disturbance secondary to liver failure. It is impossible to evaluate operative risk with any degree of accuracy twenty-four or forty-eight hours after a massive hematemesis for the obvious reason that one cannot determine the true status of liver function. Encouraged by the results following an increasing experience with balloon tamponage, we take the view that suture of varices is rarely indicated as an emergency or semiemergency procedure.

Reinflation of the balloon with maintained tamponage is the simplest and safest management of recurring hemorrhage, since the tendency to bleed is in itself a common sign of liver failure. Tamponage, when sustained for one week or ten days, affords an opportunity for the accumulation of accurate data on the status of the patient and of liver function, upon which to base a decision as to future management. Furthermore, much can be done to improve the status of the patient during the period of tamponage. We have illustrated (see Fig. 1) a nasogastric balloon tube* that is well suited to prolonged balloon tamponage. It is equipped with a large central lumen for aspirating stomach contents and feeding. The tube should not be connected for continuous gastric aspiration because this causes excessive depletion of electrolytes. Because most patients have received many transfusions which contain sodium citrate, the dietary intake of sodium is restricted to less than 1 meq. of sodium per day until it becomes established that a given patient is not disposed to the development of ascites. A wide selection of low-sodium protein concentrates is available. Patients are started early on a high-calorie, moderately high-protein, and moderately low-fat formula, given at two-hour intervals, in small quantities at first. If prefeeding aspirations of the gastric contents reveal no residue of the former feeding, the amount of feeding is gradually increased by small increments to as much as 200 to 300 c.c. In many patients, after a few days of feeding, the daily caloric intake can be increased to 2,500 to 3,000 calories.

After a seven- to ten-day period of tamponage the refractory case may be classified with considerable accuracy in one of three categories as follows:

1. Patients in whom compensation of the liver is good, and after hemorrhage there is minimal deviation from normal of the liver chemistries. The presence of severe portal hypertension is a characteristic feature of patients in this group.

2. A large group of patients with cirrhosis, with borderline or incomplete compensation. An episode of hemorrhage in these patients is likely to cause a

*Manufactured by the Davol Rubber Company of Providence, Rhode Island.

widespread break in liver compensation, with rapid increase in the size of the liver and the formation of ascites.

3. Patients with cirrhotic damage to the extent that there are not enough functioning liver cells left to withstand the effects of a severe hemorrhage.

A policy of sustained balloon tamponage identifies a sizeable number of patients as belonging to Category 1. They qualify as good operative risk, and the definitive operation of portacaval shunting is performed forthwith. The majority become identified as belonging in Category 2. Most of the patients in this category respond promptly to the favorable influence of tube feedings of a high-calorie, high-protein, high-vitamin, and low-sodium formula. As evidence of this, there is a return of appetite, gain in strength, good diuresis, diminishing tenderness in the liver, with decrease in size, clearing of jaundice and ascites. Of equal importance, there is progressive improvement in liver function. Such patients qualify at the end of a one-week or ten-day period of tube feeding as fair operative risk for shunting. However, it is our policy to extend the period of preparation one week or ten days more, because this additional preparation results in a further reduction in operative risk. The tube feedings are expanded over this period to include natural foods, such as milk, eggs, strained liver, and beef. Many such patients finally qualify as good operative risks for portacaval shunting. As would be expected, there are a number of patients in Category 2 who, after one week or ten days of tube feeding, have not responded sufficiently well to rate them as candidates for shunting at a stated date in the near future. With them one has the choice of the palliative procedure of suturing the varices or continuing with tube feedings. In those patients who have adjusted themselves to the regimen (and most of them do), it is our present policy to continue with tube feedings. It has been our experience that many patients, after two or three additional weeks of tube feeding, become candidates for shunting at a reasonable risk. The view is taken that suture of the varices is available to these patients at any time.

Certain advantages result from tube feeding in patients who are recovering from liver decompensation. The daily requirements of the types of food can be regularly administered, if necessary, in multiple small feedings, with a high-calorie, high-protein, and limited-sodium intake. It is essential that ascites be stabilized if not reabsorbed before attempting a shunting operation.[11]

Cases classified in Category 3 are patients who are in the end stage of cirrhosis. Many of them die directly following hemorrhage, even when balloon tamponage is administered promptly; or do not recover to the point of becoming candidates for suture of varices.

The good effects of these improved methods in preparing patients for shunting should be reflected in the operative mortality rate. In the first series of 117 patients operated upon, most of whom did not have the benefit of these methods, the postoperative mortality rate was 23 per cent. Continuing the series with the benefit of the preoperative procedure described, 86 additional shunts were performed in 85 patients; the postoperative mortality rate was 15 per cent. It is probable that improved methods of preparing the patients for operation were

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primarily responsible for the 8 per cent reduction in mortality, since there was no essential change in operative technique and postoperative management.

The diminishing mortality rate for shunting has confirmed and justified our early policy of expanding the basis of acceptance of patients for operation to include those having badly damaged livers complicated with hemorrhage, in whom operation would appear to be their only chance of survival. It is important at this stage of development of portacaval shunting to reaffirm clearly the previously mentioned basic indications for operation, because reports affirming a reduction in operative risk bring up the inevitable questions as follows:

1. Should shunting be performed as prophylaxis against the occurrence of hemorrhage in patients who have never had an attack of gastrointestinal hemorrhage, but who do have demonstrable varices?

2. Is ascites a primary indication for shunting?

As to Question 1, the majority of patients with varices do, at some time, bleed. Some of them fail to recover from a first hemorrhage. We take the view that they should be carefully evaluated for shunting, and operation should be recommended in those patients who qualify as good operative risks, i.e., under 10 per cent. On the other hand, it is logical to suspect that the incidence of death from a first hemorrhage is higher in poor-risk patients with badly damaged livers; and therefore, every caution should be taken against the occurrence of hemorrhage while getting these patients in condition for operation.

It must always be kept in mind that hemorrhage is not inevitable in patients with varices, and operation must be deferred in patients in whom the risk is high.

As to Question 2, if ascites were taken to be a primary indication for portacaval shunting, many unnecessary operations would be performed. Furthermore, since ascites is commonly associated with liver failure, many of the operations would be performed at a considerable risk to the patient. It has been demonstrated repeatedly that with proper diet and medication ascites can be relieved entirely in the majority of patients; or, in the more refractory cases, after months of treatment, ascites may be relieved or stabilized at a low grade not requiring paracentesis. On the other hand, in many patients ascites will stabilize (not reabsorb) under controlled hospital conditions; but subsequently, compensation cannot be maintained on an outpatient ambulatory basis.

Madden and his co-workers[1] ascribed irreversible ascites to organic obstruction to the hepatic veins (outflow tract of the intrahepatic vascular system) due to fibrosis. If this is true, it may be that repeated hepatic biopsies during the early phase of treatment will indicate irreversibility of ascites. A shunting operation should never be performed for the sole indication of ascites, except in those patients in whom it has been proved beyond doubt that the ascites is irreversible.

Unfortunately, measures designed to drain off ascitic fluid into the abdominal wall tissues or saphenous vein have not succeeded. Many attempts to promote the development of additional collateral channels between the portal

and systemic systems of veins such as omentopexy alone, or in association with scarification of the liver and diaphragm,[12] have failed to relieve ascites of the irreversible type. This is so even though what would appear to be adequate additional collateral veins have been observed to develop following such procedures. Madden and his associates[1] included the use of an irritant (magnesium trisilicate) following scarification of the liver and diaphragm in two recent cases. They visualized the "formation of an artificial bridge between the portal and systemic veins by the application of magnesium trisilicate powder to abraded areas over the superior surface of the liver and the inferior surface of the diaphragm." Occasionally one encounters patients with intractable ascites in whom there is abundant evidence of highly developed collateral circuits. Patients who have markedly dilated superficial abdominal collateral veins and large esophageal varices demonstrated by esophagram or esophagoscopy would appear to have adequate collateral veins, but the question of sluggish flow arises. Hunt demonstrated sluggish flow in the collaterals of a patient with cirrhosis who had a large (15 mm.) umbilical collateral vein by means of double venograms (taken at a stated interval). These revealed sluggish flow in the umbilical vein, which measured by his method 1.4 cm. per second, compared with a speed of flow of 4.5 cm. per second in the portal vein. The speed in the latter was increased to 8 cm. per second following the establishment of a portacaval shunt. The portacaval stoma in this patient was 2 mm. larger in diameter than the umbilical vein. The portal pressure before portacaval anastomosis was 250 mm. (saline solution), and after 125. Hunt concluded with the remark: "The shunt operation, it appears, drains the portal reservoir from the bottom, whereas the collateral vessels, however large they may be, do no more than top it off."

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Early in our experience with portacaval shunting for portal hypertension we encountered the complications of ascites. In the first 118 patients operated on,[11] the incidence of ascites of some degree was 41.5 per cent. In the series of 118 patients the highest portal pressure reading was 600 mm. (saline solution) and the lowest 200 mm. (saline solution). The mean reading in the group without ascites was 400 $\pm$ 90 mm. (saline solution) and in those with ascites it was 370 $\pm$ 30 mm. (saline solution). While the portal pressure was elevated to hypertensive levels in all patients with ascites, there was no quantitative relationship between the degree of portal hypertension and the severity of the ascites. An early appreciation of this lent encouragement to the view that portal stasis (the relief of which regularly follows portacaval shunting) and not the change in portal pressure is the responsible factor in the relief of ascites of long standing following operation. Hunt's splendid work corroborates this view, namely: the speed of blood flow in the portal vein is increased from 5 cm. per second (about the average determined speed in patients who have cirrhosis of the liver) to 12 cm. per second following a direct anastomosis of the portal vein to vena cava, end to side. The normal speed of flow of the blood in the portal vein was determined to be about 10 cm. per second.

Included in our early experience were 2 well-studied patients with intractable ascites of several years' duration. These patients became ascites-free following the establishment of portacaval shunts. They gained a great deal of weight

subsequent to operation, and have lived active lives since operation, now eleven and seven years, respectively. Judging from the present status of these 2 patients' livers on the basis of hepatic function studies, they may survive for many more years. One cannot judge the future role of portacaval shunting in treatment failures on the basis of 2 well-documented patients, but the study continues and progress is being made.[11]

CHOICE OF VEINS IN SHUNTING

As previously stated, the portal vein is affected, rendering it unfit for shunting purposes, in cases of extrahepatic portal block. This leaves the splenic vein as the one best vein for shunting in patients with portal hypertension due to extrahepatic portal block. The necessity of preserving this vein for shunting, by not performing ill-advised spenectomy, has been emphasized.

In cases of portal hypertension, the result of intrahepatic portal block due to cirrhosis, both the portal and splenic veins are usually available for shunting. The portal vein, a large, husky vein, when employed in the establishment of shunts, consistently gives a higher percentage of success than does the usually smaller, more fragile splenic vein, which has a failure rate of 12 to 15 per cent. A primary threat to failure of a portal vein-to-vena cava anastomosis arises in the presence of a pre-existing thrombus in the portal vein. This complication was encountered in 9 patients. Thrombectomy was performed, followed by the establishment of shunts, in all 9 patients. In 7 of them regional heparinization was employed postoperatively for five to seven days via a small polythene tube introduced into the right gastroepiploic vein; the other end of the tube was brought out of the wound and fixed to the abdominal wall. The anastomoses remained patent in the 7 patients treated with regional heparinization. However, the 2 patients who did not receive heparin developed thrombosis of the anastomoses. Fortunately, 1 of these patients had his spleen intact, and ten days after a hematemesis gave warning of failure, a successful splenorenal shunt was established. The other patient, whose spleen had been previously removed, died of hemorrhage.

A portal vein-to-vena cava anastomosis can be achieved more quickly than the average splenorenal shunt, and in our opinion at no greater risk to the patient, provided care is taken to avoid undue hemorrhage and injury to the major hepatic lymph channels.

The portal vein-to-vena cava anastomosis decompresses the portal system more effectively than the splenorenal shunt. There are instances when the splenic and renal veins are of comparably good size in which, following anastomosis, a drop in portal pressure of a magnitude equaling the fall obtained following portal vein-to-vena cava anastomosis results; but, the fall in pressure averages greater when the latter type of portacaval shunt is employed. The portal vein-to-vena cava anastomosis more effectively relieves stasis in the portal system than the splenorenal shunt. Hunt[4] demonstrated this well by measuring the speed of blood flow in the portal vein of patients with cirrhosis before and after establishing the two types of shunts. He reported the results as follows: the average determined speed of about 5 cm. per second in patients with cirrhosis

was increased to 12 cm. per second (average) following a direct anastomosis of the portal vein-to-vena cava, whereas following a splenorenal shunt, the speed was increased to but 7 cm. per second (average). The normal speed of blood flow in the portal vein was determined to be about 10 cm. per second. The presence of a very large spleen and evidence of excessive depletion of platelets and anemia are factors which favor splenectomy and the use of the splenic vein in a given case.

Splenoportography, or visualization of the portal system and collateral anastomotic channels by x-ray following injection of an opacifying medium (Urokon) directly into the spleen, has been employed to demonstrate the site of portal block. Experience has shown that brisk bleeding may occur at the needle puncture site in the spleen; and, therefore, it is not safe to employ the method except in the operating room just prior to, or following, opening of the abdomen.

An accurate method of determining patency of a portacaval shunt would be a valuable adjunct, particularly in patients in whom occlusion of a shunt is suspected. Encouraging results are being obtained by Deterling, Powers, and Bhonslay[13] employing radioactive sodium as follows: radioactive sodium is introduced into the rectosigmoid and the transit time for the material to reach the brachial artery is recorded. Tests performed on dogs before and after opening portacaval shunts revealed a marked decrease in transit time (values above 35 seconds before and below 20 seconds after opening shunt). In patients with portal hypertension the transit time from the rectosigmoid colon to the brachial artery ranged from 55 to 130 seconds. After portacaval shunting there was an appreciable shortening of the transit time in all patients with open shunts; most of the values ranged between 25 and 30 seconds.

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FOLLOW-UP RESULTS

The establishment and maintained patency of an adequate portacaval shunt protects the patient with cirrhosis of the liver from untimely death due to hemorrhage, and protects the liver from the deleterious effects of recurring hemorrhage and wasting ascites. Under the favorable influence of a continued medical-dietary regimen, following operation, liver function may and often does improve.

Thirty-three deaths have occurred during follow-up on 163 patients (20.2 per cent). Eighteen deaths (54.5 per cent) resulted from failure of the liver due to cirrhosis. In 5 patients (15 per cent) death resulted from hemorrhage due to shunt failure. A splenorenal shunt had been established in 4 of the patients. The fifth patient had occlusion of a portal vein-to-vena cava anastomosis. In this case the operation had followed removal of an old thrombus from the portal vein, and regional heparinization had not been employed postoperatively. Ulcer of the duodenum was the primary factor in the cause of death in 4 patients (12 per cent). The presence of common duct stones was a contributory factor in the cause of death in 2 patients (the over-all incidence of common duct obstruction in 203 cases was 5.9 per cent).

The latest follow-up information would indicate that liver function is comparatively good in 50 per cent of the living patients.

SUMMARY

Portacaval shunting for the relief of portal hypertension and portal stasis has proved to be an effective, rational, and relatively safe procedure to protect patients from untimely death due to hemorrhage, and to protect the liver from the deleterious effects of recurring hemorrhage and wasting ascites.

A characteristic feature of cirrhosis is the architectural distortion which, with progressive disease, inevitably leads to obstruction to the inflow of portal blood. Obstruction to portal blood flow frequently results in the development of esophageal varices which are disposed to rupture, causing hemorrhage. In patients having portal block, portal venous pressure is elevated. The establishment of a portacaval shunt, employing either the portal vein anastomosed directly to the vena cava, or the splenic vein (following splenectomy) anastomosed end to side with the left renal vein, affords a large channel having a low resistance to blood flow, and capable of shifting a large volume of blood rapidly from the high-pressure (portal system) to the low-pressure (caval) system, and thereby effecting a reduction in portal pressure with relief of portal stasis.

In 1943, we undertook a study of portacaval shunting. To date the experience has been expanded to embrace 262 shunted patients. The site of portal block was intrahepatic, due to cirrhosis of the liver, in 203 patients (77.4 per cent) and extrahepatic, due to a block in the portal vein outside of the liver, in 59 patients (22.6 per cent). The shunting procedure was accomplished in the first 117 patients having cirrhosis of the liver with a postoperative mortality rate of 23 per cent. The mortality rate in the remaining 86 patients was 15 per cent. The decrease in mortality rate is attributed primarily to improvement in the preoperative preparation of patients.

The high incidence of liver failure in association with hemorrhage is discussed with special reference to emergency management. An efficient nasogastric balloon tube is presented with detailed instructions on its use for the emergency arrest of hemorrhage and in the preparation of patients for operation. Patients who show a tendency to immediate recurrence of bleeding after the customary four days of balloon tamponage and tube feeding are classified as refractory, and treatment is continued until their status can be ascertained on the basis of clinical behavior and dependable hepatic function tests. Many, after one week or ten days of tube feeding, are proved to have well-compensated livers, their tendency to hemorrhage being the result primarily of severe portal hypertension. In such patients the definitive operation of portacaval shunting can be carried out forthwith. More difficult patients are those in whom ten days or two weeks of treatment does not relieve impairment of liver function, and in whom the operation must be postponed or abandoned. It is with this group that suture of the esophageal varices may be carried out at a propitious time. Our present policy, however, is to continue with tamponage and tube feeding in those patients who are adapted to it, because after a few more weeks, many will improve to a point that shunting may be proceeded with at a reasonable risk.

Early in our experience with portacaval shunting for portal hypertension the complication of ascites diagnosed clinically was encountered in 41.5 per cent of the cases. The presence of ascites may in itself be taken as a sign of decom-

pensation of the liver, and, if unstabilized before operation, materially increases operative risk. Portal pressure was elevated to hypertensive levels in all patients with ascites; however, there was no quantitative relationship between the degree of portal hypertension and the severity of the ascites. An early appreciation of this lent encouragement to a view that portal stasis (the relief of which regularly follows the establishment of a portacaval shunt) and not the change in portal pressure was the responsible factor in the subsidence of ascites in a few early cases of long-standing ascites operated upon. This view is corroborated by the work of Hunt, who has shown that the speed of blood flow in the portal vein is increased from 5 cm. per second (about the average determined speed in patients with cirrhosis of the liver) to 12 cm. per second following a direct anastomosis of the portal vein to vena cava, end to side. The normal speed of flow of the blood in the portal vein was determined to be about 10 cm. per second.

The indications for portacaval shunting and the evaluation of operative risk with respect to hepatic function tests are discussed.

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Editorials

PAIN—THE NEUROSURGEON'S VIEWPOINT

In the long course of chronic disease, pain often becomes a major problem for both patient and physician. In protracted illnesses, especially one which is recognized to be incurable, the patient soon learns that for his primary disease he can get only lip service but for pain he can get attention, sympathy, and drugs which may lift his spirits from a bed of woe. Pain, then, soon comes to be associated and synonymous with his illness, so that even when his discomfort is minimal or absent, he continues to require drugs. This type of patient demands his sedation every three hours around the clock, even though he displays no manifestation of pain. In other cases, pain is really the mental suffering of the individual threatened by multilation of his ego. It is then of prime importance that the physician understand the true nature of a patient's pain, since the therapy of the conditions mentioned varies greatly.

Assuming that the pain is intractable and not amenable to direct attack, a number of factors remain to be considered before deciding upon the best means of treatment. One of the first is the life expectancy of the patient. If only a few months remain, it may be better to continue with medicinal therapy, even though it means addiction. Although narcotic drugs become ineffectual eventually, there are now enough preparations to carry most patients in relative comfort for several months. Only if a patient survives the rigors of an operative procedure for the relief of pain for six months will he or she really appreciate the benefits.

Then one must consider the social and economic condition of the patient. Operative procedures may require long and costly periods of hospitalization and convalescence which may deplete the financial resources of a marginal family. If the outcome is inevitable, such expense may not be justified and may seriously handicap the family after the death of the patient, who might be equally well relieved of his suffering by conservative and cheaper means. If the illness is not a fatal one, it probably will be well worth while tightening the family budget to get a wage earner back to work, or a loved one restored to health.

After such an evaluation of not only the physical, but also the psychologic, economic, and social factors, one may consider the neurosurgical procedures available for the relief of intractable pain. These are applicable for only certain pain syndromes, and may fail to give a desired result if applied in an unsuitable case.

Sympathectomy.—In selected cases of special pain syndromes, operations on the sympathetic nervous system give excellent results. In vasospastic conditions, such as Raynaud's disease, or vascular disease with vasospastic ele-

ments, such as Buerger's disease, sympathectomy relieves pain largely by increasing the blood supply.

Causalgia is particularly amenable to sympathectomy, and even the related syndromes of Sudeck's atrophy, etc., may be relieved to some extent by sympathetic interruption. It is usually advisable to carry out a preliminary chemical block of the involved part as a diagnostic and prognostic test. If temporary relief is not obtained the case should be reviewed for diagnosis and therapy, since sympathectomy has only a slight chance of giving satisfactory results. If the procaine injection in the appropriate sympathetic ganglia does give relief, good results may be expected from the surgical sympathectomy in almost all cases.

For causalgia of the upper extremities a preganglionic interruption of the thoracic chain below the third ganglion with section of the rami communicans to the second and third ganglia is usually satisfactory. Removal of the second or third lumbar ganglia relieves most cases of causalgia of the lower extremities, but in some, the site of injury may have to be denervated for relief.

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Anginal pain may be markedly decreased or eliminated by resection of the upper four thoracic sympathetic ganglia on both sides. Occasionally resection of the left sympathetic ganglia alone will be effective. In a series of seventy-one cases, Lindgren and Olivecrona[1] reported complete relief in 43.7 per cent of cases and partial relief in 40.8 per cent. Even myocardial infarction, the eventual cause of death in most cases, causes no pain. This procedure deserves more popularity than it at present enjoys, and should not be advised against for fear that the patient will exert himself unduly if his safety warning—myocardial pain—is removed.

Abdominal distress may also be relieved by sympathetic denervation. The excruciating pain of chronic pancreatitis is usually eliminated by splanchnicectomy on the left side. Presacral neurectomy is valuable in the treatment of pain associated with dysmenorrhea, endometriosis, inoperable carcinoma of the genitals, and pelvic pain of unknown etiology. In dysmenorrhea, Phaneuf[2] reported good results from presacral neurectomy in 50 per cent of cases and some improvement in 29 per cent in a series of sixty-eight cases.

Rhizotomy.—The best known and most satisfactory rhizotomy is the classic retrogasserian neurectomy for trigeminal neuralgia. It is a simple operation, well tolerated even by the aged. The price for the relief of pain is anesthesia of the previously involved portion of the face. The sensory loss is usually not unbearable, but occasionally paresthesias are quite annoying. Fortunately this complication occurs in less than 5 per cent of cases. Keratitis is rarely seen now that a subtotal avulsion of the root has become standard practice. Facial paralysis occurring in about 6 per cent of patients usually is temporary and, unless the cornea has been denervated, is not a serious complication. Pain from malignancies of the head may also be relieved by trigeminal neurectomy, but often some recurrence of pain detracts from the result.

To prevent the distressing paresthesias which sometimes follow a retrogasserian neurectomy, Sjöqvist[3] introduced section of the descending root of the trigeminal nerve. This procedure has a definite place in the treatment of

intractable facial pain, but it has a somewhat higher mortality than the classic retrogasserian neurectomy. Unfortunately the results of this section are less certain than those of the neurotomy and not uncomplicated by paresthesias. Decompression of the posterior root, which also causes no sensory disturbances, may prove to relieve many cases. Eventually medical therapy (stilbamidine now seems promising) may eliminate the need for surgery in this condition.

Section of spinal posterior roots for the relief of pain has not proved to be generally satisfactory. To be sure of complete denervation of the given dermatome, at least two and sometimes three roots above and below the dermatome must be sectioned. This produces a large anesthetic zone, which often gives rise to distressing numbness. Moreover, a denervated limb becomes useless. To avoid these unpleasant sequelae, one or more roots of the involved area are left intact. This relieves most of the pain but prevents the undesirable numbness and virtual paralysis.

Cordotomy.—Spinal section of the pain-carrying fibers—the spinothalamic tract—leaves intact touch so that pain may be abolished without numbness. Anterolateral cordotomy is a standard and excellent procedure for the relief of pain (White and associates), although because of technical operative difficulties the results are not always as good as desired. The most common causes of failure are (1) improper position of the incision, either too far anterior to the dentate ligament in cases of pelvic pain or failure to carry the incision far enough anteriorly in thoracic pain, (2) failure to make a bilateral cordotomy for abdominal malignancy with unilateral pain, (3) improper selection of cases, and (4) too great a delay in performing the operation. Unless the patient has a life expectancy of at least six months he or she will not live long enough to recover from the discomfort of the operation and the annoyance of urinary retention, which is a transitory complication. A progressive cachexia added to these distressing factors may make life unbearable even though the pain has been eliminated.

Spinothalamic tractotomy is especially recommended for nonlethal painful conditions such as arthritis, tabetic crises, chronic pancreatitis, and abdominal pain of unknown etiology. In slow-growing malignancies it is valuable, but in rapidly progressive neoplasms its transient postoperative sequelae make it less desirable.

The cordotomy may be carried out in the upper thoracic or upper cervical region. Usually a sufficiently high level may be obtained by a properly placed incision at the first or second thoracic segment to relieve pain in the lower chest or abdomen. If it is desired to denervate the upper chest or arm, a cervical cordotomy must be performed. This is not a formidable procedure and in fact has certain advantages over the thoracic cordotomy in that there is somewhat less chance of damaging the pyramidal tracts and consequently less weakness and urinary disturbance.

The cordotomy is usually carried out under local anesthesia, for the patient must cooperate in sensory testing to tell the surgeon when the incision has been made sufficiently deep. Usually analgesia about 4 to 5 dermatomes above the

site of the pain is desired at the operating table, for one must expect that the level will fall from 1 to 3 dermatomes within a few weeks.

Following the cordotomy there is usually a severe constipation for several weeks, rarely incontinence due to an absence of feeling about the rectum and anus. Urinary retention is present in bilateral cordotomies for from two to six weeks, but gradually recedes. Some degree of weakness of the legs is the rule, and a patient commonly has to be taught to walk by the aid of parallel bars. These sequelae prevent the patient from returning to a normal existence for approximately three months, but usually after that time the patient becomes gratefully aware of his freedom from pain. In males there is often, but not always, an impotence, usually transient, which rarely causes trouble since most patients requiring cordotomy have long since lost their potency for one or another reason.

Interruption of the spinothalamic tract may be carried out at the medullary, mesencephalic, or thalamic level, but these rostral operations ordinarily have little to recommend them over the spinal sections.

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Prefrontal Lobotomy.—Considerable emphasis has been placed in the past ten years upon the value of prefrontal lobotomy in the treatment of intractable pain. If mental suffering is prominent the distress may be eliminated temporarily or permanently by bilateral prefrontal lobotomy. The patient still appreciates the painful stimuli but no longer complains spontaneously of his discomfort. In most cases, there is a certain amount of apathy and mental confusion lasting for a few months or permanently. Some patients lose all initiative; others become "slap-happy." One woman, some three years after a standard lobotomy for postneurectomy paresthesias, giggled as she stated that she still had painful feelings in her face. Her husband was satisfied with her condition for she no longer pestered him with her complaints but sat around the house quite content to do nothing. Her disposition was cheery, but time meant nothing to her. If allowed to go downtown alone, she would get lost. Her memory was poor for all events since her operation, but good for previous experiences. Her previous meticulous nature had been exchanged for careless and sloppy habits.

To avoid these unpleasant sequelae, modified prefrontal lobotomies have been advocated. Topectomy—a resection of the tips of the frontal lobes—may be carried out bilaterally without producing marked derangement of the personality. However, most neurosurgeons consider this a formidable procedure and prefer a simpler operation on the frontal lobe. By unilateral prefrontal lobotomy, ipsilateral or contralateral to the pain, temporary relief from pain is obtained in the majority of cases. After three or four months at least 75 per cent of the patients are suffering as severely as ever.

Injection of procaine into the deep white matter of the frontal lobe may be followed by relief of pain for weeks or months. Since the procedure may be repeated through the burr holes if the pain recurs, the patients may be kept comfortable for life if the expectancy is not long. Such a chemical prefrontal lobotomy ordinarily is not associated with mental confusion and at times provides welcome relief for the sufferer from carcinoma.

The place and limitations of prefrontal lobotomy are not too clearly defined, but it is evident that the first reports of this procedure were prematurely enthusiastic. With this realization, the oft-repeated but apparently infrequently followed advice that prefrontal lobotomy should be used as a last resort deserves more serious consideration. It is, indeed, unfortunate to render a person with indefinite life expectancy "slap-happy," irresponsible, and unable to take part in social or family life, when other techniques might relieve pain without deleterious side effects.

What course, then, should be followed in the treatment of intractable pain? In certain syndromes, specific techniques are indicated, such as retrogasserian neurectomy for trigeminal neuralgia, and sympathectomy for causalgia. In the more general pain syndromes, however, specific measures are not available. If the life expectancy is not more than three or four months, analgesic and narcotic drugs are preferable to any surgical procedure on the central nervous system. A chemical prefrontal lobotomy might relieve the suffering and eliminate the necessity of constant narcotics. If the expectant life is six months or more, an appropriate section of the spinothalamic tract offers the best chance of complete relief with few untoward sequelae. It is then apparent that the relief of intractable pain requires a nicety of judgment on the part of the physician, who must weigh the medical, economic, and social factors in formulating the best therapy.

A. EARL WALKER

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THE GENETIC BACKGROUND OF CHRONIC DISEASES

If we are to examine the genetic aspects of such chronic diseases as atherosclerosis, diabetes, or cancer, where the etiologic factors are yet obscure, it will be well first to consider the nature of the genetic basis of some better understood pathologic conditions. As a first principle it must be emphasized that hereditary and environmental etiologic factors usually coexist and interact in each morbid condition. No error is more common or more fatal to clear thinking than to suppose that if a condition is hereditary it cannot be produced, or even modified, by an infectious or dietary agent; and, conversely, that if a condition is clearly due to an infectious agent or to a dietary deficiency, it cannot at the same time be conditioned by the genes. There are, for example, two genetic strains of rabbits that differ, when kept on a diet rich in xanthophyll, in the color of their fat, the one producing yellow, the other only white fat; yet, when shifted to a diet lacking xanthophyll, both strains produce only white fat. The difference between strains seen on the full diet is hereditary; but within one of the two strains, the difference in fat color is clearly of dietary origin. Let us also recall the instance of tuberculosis, so clearly due to an infectious organism. Yet Kallmann and Reisner (1943), in their remarkable studies of twins, showed equally clearly that tuberculosis mortality and morbidity vary with degree of genetic relationship, over and above the factor of shared home environment. Both of these examples inform us that the genes, acting as they must within a certain developmental and environmental framework, rarely produce absolute effects, but instead determine an individual's capacities, the nature of his reaction under specified conditions.

A second most important principle to fix in mind is the very common ramification of the effects of a single genetic change. Often the effects are apparently so unrelated as to have no conceivable connection with one another. Yet, if a single gene can be shown to produce these several effects, they must in some way be interrelated. Many, if not most, genes produce their initial effects during embryonic life, and there is plenty of opportunity for a primary effect to produce secondary effects, and these, in turn, tertiary and still further orders of effects. For example, Fig. 1 shows some of the ramifying effects of the Pelger anomaly, which is a human pathologic condition exactly duplicated in the rabbit (Nachtsheim, 1950). In man and rabbit it is further inherited in an identical way, although in the rabbit the homozygous Pelger condition is known, whereas in the human species the condition is so rare that only one individual carrying a double dose of the gene has so far been found. The Pelger gene in single dose causes the nuclei of the granular leukocytes to remain simply bilobed, instead of becoming characteristically trilobed or polymorphonuclear. In double dose, in the rabbit, it results in a simply spherical nucleus in these cells, which appear to be the only blood cells affected. However, the homozygous condition is

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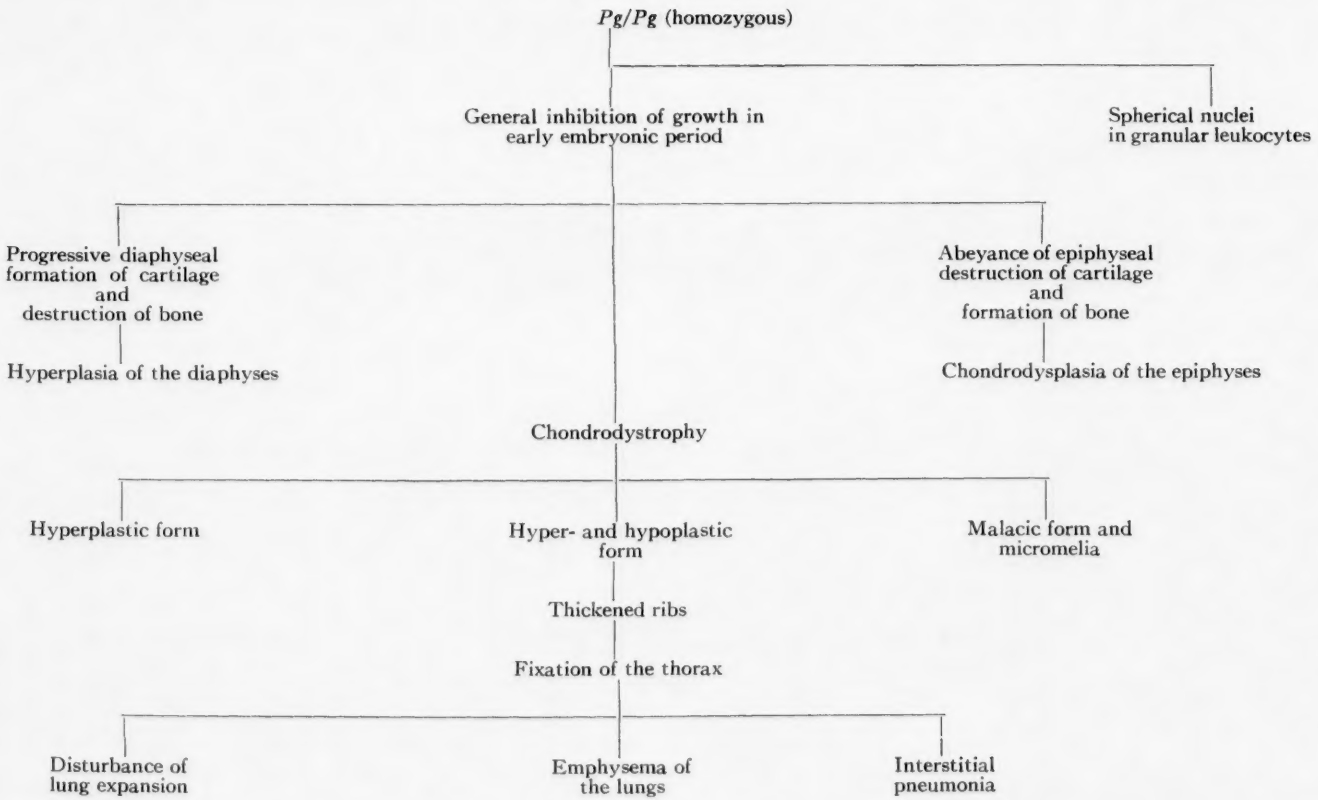
Pg/*Pg* (homozygous)
General inhibition of growth in early embryonic period
Spherical nuclei in granular leukocytes
Progressive diaphyseal formation of cartilage and destruction of bone
Hyperplasia of the diaphyses
Abeyance of epiphyseal destruction of cartilage and formation of bone
Chondrodysplasia of the epiphyses
Chondrodystrophy
Hyperplastic form
Hyper- and hypoplastic form
Malacic form and micromelia
Thickened ribs
Fixation of the thorax
Disturbance of lung expansion
Emphysema of the lungs
Interstitial pneumonia

Fig. 1.—The ramifying effects of the single gene responsible for producing the Pelger anomaly.

further characterized in the rabbit by skeletal defects that start to appear in early embryonic life, lead to chondrodystrophy and, as the figure shows, terminate frequently by one or another route in early death. Genetics here points to a problem still to be solved by the anatomist and histologist: what is the unknown connection between the shape of the nuclei of the granular leukocytes and the development of the skeleton? A similar example is afforded by the interesting anomaly known as phenylpyruvic oligophrenia (also called phenylketonuria), to be discussed more fully below. In this condition the normal oxidative breakdown of phenylalanine by way of tyrosine is blocked, and phenylpyruvic acid is excreted in the urine. What connection is there between this seemingly harmless metabolic product and the low-grade imbecility or idiocy that is invariably associated with it?

A third important aspect of this relationship between gene and character offers another experimental toehold. This lies in the fact that many conditions, which appear from an anatomic, clinical, or physiologic viewpoint to be identical, may by genetic studies be shown to differ. As the widely known studies made in biochemical genetics within the past fifteen years have indicated, most, if not all, single gene differences between the normal and a mutant type block or alter single biochemical steps in the metabolic pattern. This may be illustrated effectively by a chart (Fig. 2) showing the pattern of phenylalanine and tyrosine breakdown in man. The simple Mendelian recessive already mentioned (phenylketonuria) blocks one particular step; recessive alcaptonuria, in which the urine turns black upon exposure to air, is produced by a second genetic block; and albinism, also generally recessive, blocks a specific third step. Even a fourth specific block in this relatively circumscribed biochemical area is known, as indicated; but it has been reported only in three individuals, so that the inheritance of the condition is not certain. In at least one of these hereditary conditions, phenylketonuria (Jervis, 1953, 1954), and perhaps in alcaptonuria also, it has been shown that the genetic block is due to the failure of the individual to produce the specific enzyme required for the conversion. Such may often be the nature of the block; yet studies in other organisms show that the specific enzyme involved may indeed be present in certain genetically blocked mutant types, but that it has been altered so that the rate of the reaction is changed. Or the normal enzyme may be present, but, conceivably, a specific coenzyme may be missing locally. At any rate, mutation can change the site of action, that is to say, the tissue specificity, of the enzymatic conversion of substrate into product.

Apart from the intimate relation of genetics to biochemistry thus indicated, another instructive point lies in the fact that albinism is of several different genetic types. There is a dominant albinism, and there are albinisms with only partial extension over the body. This genetic diversity, even when the phenotype varies no whit, implies the existence of a different biochemical basis at the primary level where gene controls enzyme. This relationship is well illustrated in some recent work of Harris and Warren (1953) on cystinuria with stone formation, long supposed to be a single clinical and genetic entity. In the population at large the amounts of cystine excreted in the urine form a

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normal distribution, whereas in the selected cystinurics and their relatives Harris found a bimodal type of distribution. Further analysis revealed two types of families with cystinurics. In one sort the relatives fall into the normal distribution for the general population. In the other they form an intermediate group with a mode between that of the cystinurics and the average for the general population. In the first case, the gene responsible for cystinuria appears to be a simple recessive, whereas in the second case heterozygous individuals are distinct from both normals and cystinurics. Two genes must be involved, one

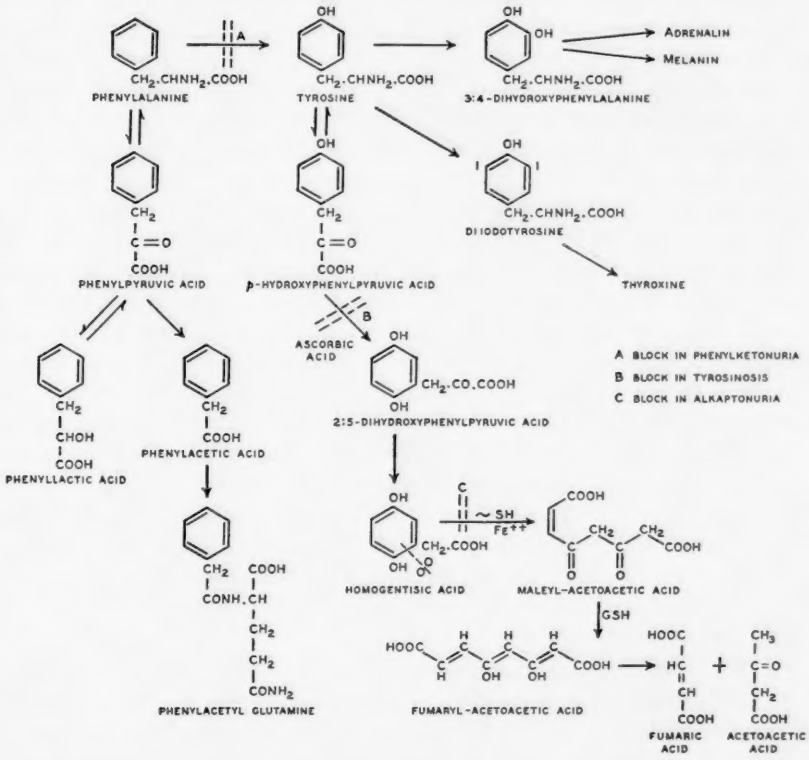

Fig. 2—The pattern of phenylalanine and tyrosine breakdown in man, to show the positions of various genetic blocks in the metabolism.

completely recessive, the other intermediate. It is not known at present whether these are alleles or differ in chromosome location. From what we do know of inherited characters in other species, it seems very likely that many genes may produce the same end effect, and perhaps also in this case distinct genes are to be expected. The value of learning this lies in the indication that the metabolic path is probably blocked at different points in the different genetic cases; and biochemical investigation can proceed to distinguish them and enable us to learn more about the several steps in the production of the clinical condition.

It should not need to be pointed out that this may in turn greatly enhance the accuracy of diagnosis and the power of therapy.

Turning now to the specific applications of these concepts and principles to chronic diseases, only a few examples can be discussed at this time. As to *atherosclerosis*, we may note first of all that deposition of lipids in the aorta and coronary vessels is part of a broader phenomenon, the deposition of lipids in many sites, and, especially, besides the blood vessels, in liver and skin. Xanthomatosis or xanthelasma are often associated with coronary disease and atherosclerosis, and xanthoma tuberosum and xanthomatosis have often been described as hereditary. Adlersberg, Parets, and Boas (1949) have demonstrated that hypercholesterolemia is more of a key factor than the actual deposit of lipid or cholesterol plaques in the skin and eyelids (xanthoma and xanthelasma, respectively). In the entire families of 35 persons with xanthomatosis (201 persons), hypercholesterolemia was present in 60 per cent, coronary atherosclerosis in 40 per cent, xanthelasma and corneal arcus in 30 per cent and 18 per cent, respectively, and tuberous xanthoma was the least frequent stigma (12.5 per cent). There is now very good evidence, taking idiopathic hypercholesterolemia as the basic trait rather than the less frequently manifested stigmata, that it is produced by a single dominant gene. Even with high blood cholesterol as the criterion of the inherited condition, however, there is evidence of a lack of complete penetrance. That is to say, some individuals carrying the dominant gene may fail to reveal a high blood cholesterol level, even as some fail to develop coronary atherosclerosis, still more fail to develop xanthoma, and so on. This provides clear evidence that other factors can alter the manifestation of the main gene's effect. These might be other genes, modifiers, so to speak; or they might be factors external to the genotype altogether, for example, dietary differences. The total picture begins to look like the chart of effects produced by the Pelger gene, and reminds us that in our analysis we may still be far away from the primary action of the dominant gene concerned. The high level of blood cholesterol observed may itself be a secondary or tertiary effect of that primary action.

To follow up this idea, let me recall the finding by Best and his associates that depancreatized dogs do not develop fatty livers if they are fed excess choline. A recently published report from the same group (Wilgram, Hartroft, and Best, 1954) carries this analysis considerably farther. In a high percentage of cases rats placed on a choline-deficient diet develop heavy lipid deposits in the coronary arteries and aorta, while controls remain entirely free. Many of the affected rats die of vascular lesions. The previous work of this group has led to knowledge of certain "lipotropic" factors that act like choline in preventing the fatty infiltration of organs. Some, like choline, apparently act as donors of methyl groups. Methionine presumably acts by virtue of its role in the synthesis of choline itself. Other lipotropic agents, such as aminoethanol and triethylcholine, lack labile methyl groups, but act like choline in the synthesis of phospholipids. One may, therefore, conjecture that the primary disorder of metabolism in "idiopathic hypercholesterolemia" lies not in cholesterol synthesis or breakdown, but perhaps rather in phospholipid synthesis. If there is an inadequate

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synthesis of phospholipids in the liver, an excessive deposition of fats would probably occur there, and perhaps the formation of cholesterol in abnormal amounts would be a by-product, since there is evidence that fatty acid synthesis and cholesterol synthesis compete for the two-carbon intermediates needed by both. These possibilities not only raise problems for the biochemist to attack, but open numerous paths for the genetic approach. One would like to know whether there is any choline abnormality connected with idiopathic hypercholesterolemia. Do people differ genetically in ability to absorb choline from the diet? or in ability to synthesize it from methionine? Is there any familial concentration of persons with abnormal phospholipid metabolism in the families with idiopathic hypercholesterolemia?—and so forth.

One more interesting point derived from the data of Adlersberg and his associates (1952) may be mentioned. This is the very much higher incidence of the gene for disturbed lipid metabolism among Jews (21 per cent) than among non-Jews (9 per cent), in the sample of hospital patients studied. At the same time, the frequency of hypercholesterolemia among the sibs and children of the Jewish probands was no higher than among the non-Jews. The latter fact indicates that "environmental factors such as different occupations, housing and dietary patterns are not of decisive importance in determining the presence or absence of hypercholesterolemia." On the other hand, the ethnic difference in incidence is what we are led to expect by the study of the variations in gene frequencies in different populations and races, and constitutes further evidence of the importance of the gene in the incidence of atherosclerosis.

It would be a violation of everything said heretofore to suppose that all atherosclerosis is attributable to one particular gene and one particular sequence of errors in metabolism. Enough has been said, however, to show how the human geneticist looks at this type of problem, and how fruitfully work along genetic, as well as anatomic and biochemical, lines may lead to the eventual understanding of this ever more dominant killer of mankind.

The role of genetic factors in the occurrence of various types of *cancer* has received much attention. Certain types, such as multiple neurofibromatosis and multiple polyposis of the colon, are produced by single dominant genes of high penetrance; but for the more common types of cancer, such as cancer of the breast, uterus, or prostate, or for leukemia, the exact role of the genes is not so clear. There is a twofold or threefold increase in the incidence of breast or uterine cancer among the closest female relatives of index cases. Rather more striking is the lack of complete concordance among monozygous (one-egg) twins, a clear indication that the genetic factors involved are not omnipotent but that other etiologic factors may alter the outcome. Especially striking is the high degree of similarity in the type of tumor seen in monozygous twins when both are affected. The concordance in type reaches nearly 100 per cent, whereas in dizygous twins of the same sex it is less than two-thirds, according to a study made by Madge Macklin (1940).

In spite of the biases inherent in the collection and interpretation of twin data, recently so much discussed (see Price, 1950; David and Snyder, 1954;

Neel and Schull, 1954), such studies can be invaluable in the investigation of the chronic diseases. The mere determination of the concordance and discordance between co-twins can be made much more valuable by the inclusion of similar data for other degrees of relationship, such as full sibs, half-sibs, parents, step-sibs, spouses, and randomly selected control individuals, just as Kallmann and Reisner did in their study of tuberculosis and as Kallmann has continued to do in his studies of the psychoses (Kallmann, 1953, 1954). Far more valuable, in the long run, are the uses to which co-twin material can be put in the study of norms and capacities of reaction. These possibilities, which I have discussed elsewhere (Glass, 1954), are excellently exemplified in the studies of Lennox and Jolly (1954) on seizures, brain waves, and intelligence tests of epileptic twins. The "normal" monozygous twin of an epileptic constitutes as good a subject as possible for the study of similarities in reaction capacity, such as the remarkable resemblance of the brain waves, and for obtaining insight into differences traceable to past experience and to external etiologic factors. Thus, so long as there is no prior brain damage, the IQ scores of monozygous twins remain extremely alike, whether both or only one member of each pair has experienced seizures. But, once brain damage occurs in one twin, the intelligence scores of the co-twins assume a considerable difference. The experimental and continuous study of the monozygous twins of individuals with a chronic disease, together with the study of heterozygous carriers of genes that in the homozygous condition produce pathologic effects, promise to become among the most significant ways in which the applications of genetics to chronic disease can bring about fruitful results.

Aging itself can be shown in our experimental animals to be a part of the norm of reaction to the environment, and to be under the influence of the genes. Some strains are inherently long-lived; others seemingly wear themselves out within a much shorter life span. There is evidence that this is true in the human species also, for Kallmann (1953) has found that the deaths of co-twins more than 60 years of age are on the average more than twice as many months apart among dizygous twins of the same sex as among monozygous twins. The difference "falls largely into the age group 60-74, disappearing beyond age 75." That being so, it seems probable that it is mainly a product of the similar response of the identical co-twins to chronic diseases, rather than the result of a similarity in the "healthy" but inevitable wearing out of the body's organs and tissues. Yet even here the distinction must not be drawn too fine. Chronic disease attacks the constitutionally weaker organs. The vicissitudes of life find their most vulnerable targets in the structural, metabolic, and biochemical lesions initiated by the genes.

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VECTORCARDIOGRAPHY

Many physicians, including a large group of capable internists and cardiologists, have been aware of the interest in vectorcardiography and vector methods in the past few years but have been confused by the technical aspects of this specialized field and by the claims of some vectorcardiographers. Some of these physicians are quite familiar with ordinary electrocardiograms and would like to know if vectorcardiography is truly a new technique that makes it possible to recognize cardiac lesions with greater ease and certainty then can be done with conventional records. This article attempts to answer this question by pointing out in the simplest possible terms what vectorcardiograms are, how they must be taken, and their relation to ordinary electrocardiograms.

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Although Wilson and Johnston[1] originated the term "vectorcardiogram" in 1938, records of this kind were known to Einthoven[2] and were constructed from standard electrocardiograms in 1920 by Mann.[3] Since limb leads were exclusively employed in this early work, all the vectorcardiograms described by these investigators were in the frontal plane, and it was only within the past twelve to fifteen years that Duchosal and Sulzer,[4] Burch and associates,[5] and many others began to record vectorcardiograms in transverse and sagittal planes, as well as in the frontal plane, making spatial vectorcardiography possible.

Vectorcardiograms may be obtained in different ways. Rough approximations of the figures can be made by inspection of conventional electrocardiograms, or more accurate records can be obtained (again from ordinary tracings) by methods described by Mann[3] and more recently by Grant and associates,[6] and finally vectorcardiograms can be recorded by use of cathode-ray oscillographs and necessary associated equipment. The last method involves the use of fairly complicated and expensive apparatus but produces in an elegant and more accurate fashion the same type of record that would be obtained by the simpler techniques. It must be emphasized that although the cathode-ray oscillograph is an instrument of precision and is capable of combining two conventional electrocardiograms to produce a vectorcardiogram more easily and accurately than can be done in any other way, the vector tracing is still derived from two more or less usual leads (from each of which ordinary electrocardiograms could be recorded) and therefore the vectorcardiogram cannot provide information about the heart that is not also present in the ordinary tracings which are combined to produce it.

It is true that phase differences not readily appreciated in conventional tracings, even if they are recorded simultaneously, are clearly revealed in vectorcardiograms, and consequently these records taken on different subjects may be somewhat different in outline, even though the conventional electrocardiograms that are taken on these individuals (and are combined to produce the vectorcardiogram) are quite similar. Fig. 1 illustrates this point and also shows how the cathode-ray oscillograph combines two conventional electrocardiograms

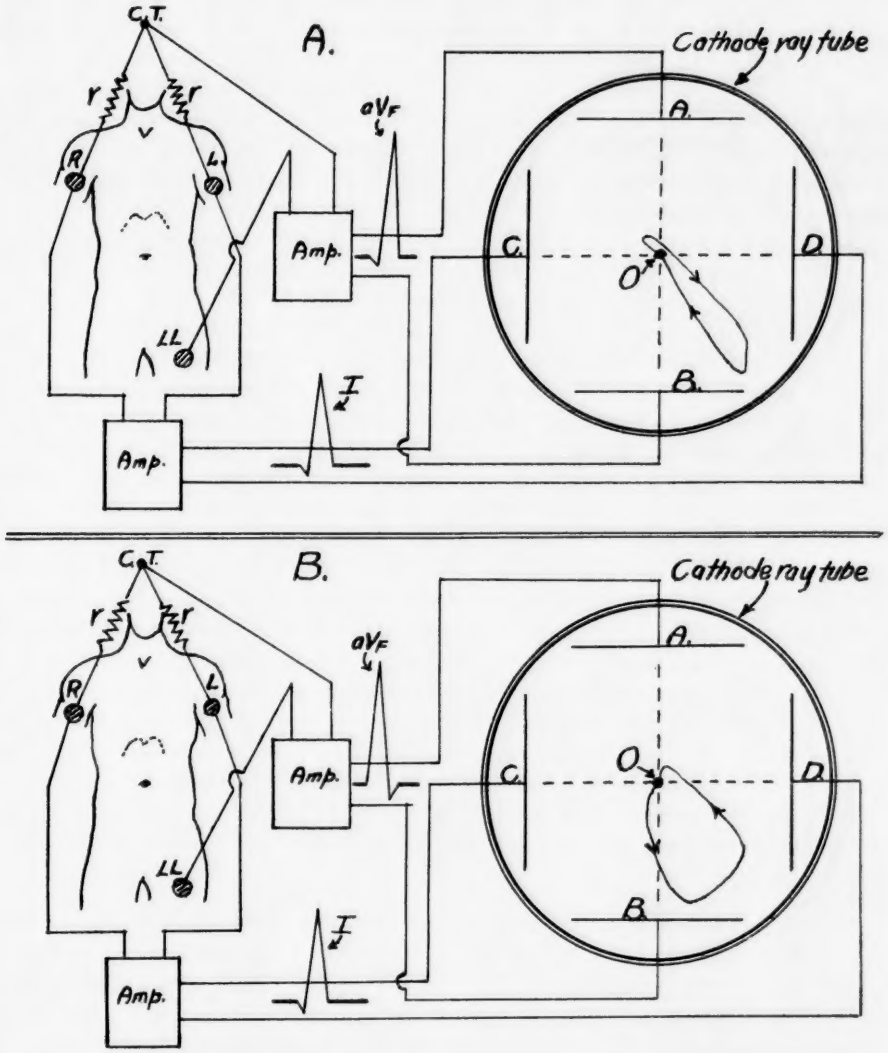

Fig. 1.—Both *A* and *B* illustrate the connections to obtain a vectorcardiogram in the frontal plane using suitable amplifiers (*Amp.*) and the cathode-ray oscillograph. In both *A* and *B*, *R*, *L*, and *LL* are electrodes on the right arm, left arm, and left leg, respectively, of a patient; the resistances *r* are equal (at least 5,000 ohms) and join to form a central terminal (*C.T.*), which is paired with the electrode on the left leg to obtain the vertical component, *AVF*. The amplified voltages of Lead I (*I*) and *AVF* are applied across the horizontal plates (*C* and *D*) and the vertical plates (*A* and *B*), respectively, of the cathode-ray tube. *O* is the neutral point where the electron beam strikes the face of the tube and causes a bright spot when no voltages exist between deflecting plates of the tube. When voltages of Lead I and *AVF* are impressed between the plates, the spot moves from the neutral position and traces out the closed loops (vectorcardiograms) drawn on the face of the tube. See text.

to record a vectorcardiogram. In order to simplify the figure, the leads for the transverse components (Lead I) are assumed to be identical, and the vertical components (*A VF*) have R waves of the same size, but in one diagram (*A*) the peak of R is late (preceded by a small Q wave) and in the other (*B*) the peak is early (followed by a small S wave). When there is a downward deflection in Lead I the bright spot on the face of the cathode-ray tube moves in a horizontal direction from the neutral point *O* toward the reader's left, and during the inscription of an upward deflection in Lead I the spot moves in the opposite direction (to the reader's right) from *O*. In both instances the distance the spot is deflected from *O* is proportional to the size of the downward and upward deflections; that is, the Q and R waves here. In an exactly similar fashion the amplified voltages from Lead *A VF* connected to the vertical plates of the cathode-ray tube cause the spot to move up and down from the neutral point. Here an upward deflection in *A VF* causes the spot to move downward, and a downward deflection in the lead deflects the spot upward. Since these horizontal and vertical movements of the spot occur simultaneously, it is clear that as it moves it will trace out closed loops that begin and end at the neutral point. The P wave, the QRS complex, and the T wave all have corresponding loops in vectorcardiograms, but we are considering only the QRS deflections and the vector counterpart here. The vectorcardiograms in Fig. 1 are in the plane established by the limb leads, that is, the frontal plane, and it will be observed that although the transverse component (Lead I) is identical for both and the vertical components (*A VF*) are similar in form, the vector figures differ not only in general outline but also because in one (Fig. 1,*A*) the spot records the loop by rotation in a clockwise direction, while in the other (Fig. 1,*B*) the rotation is counterclockwise. Some vectorcardiographers have paid a great deal of attention to the direction of rotation as a means of differentiation between important electrocardiographic conditions. This may be to some extent justified, but Fig. 1 illustrates how a small difference in one component may reverse this feature of the loops.

The vectorcardiograms in the frontal plane illustrated in Fig. 1 are obtained by combining Lead I, the transverse component of the cardiac voltages, with *A VF*, the vertical component. If Lead I were combined in a similar fashion with a lead giving an anterior-posterior or sagittal component of the cardiac electromotive forces, a vectorcardiogram in a transverse or horizontal plane would be obtained, and combination of *A VF* and the sagittal component would yield a vectorcardiogram in a sagittal plane. If vectorcardiograms in any two of the three possible planes are available, the spatial orientation of the loops which correspond to the P waves, QRS complexes, and T waves can be determined. Unfortunately, there is no general agreement regarding the polarity to be used or the conventions to be observed in the display of vectorcardiograms taken in the horizontal and sagittal planes. Recommendations covering some of these matters have been recently made by the Committee on Electrocardiography of the American Heart Association,[7] and these should help to bring some uniformity to this chaotic field.

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Several vectorcardiographers have placed great emphasis on vector figures in the horizontal plane, and rules for the recognition of bundle branch block, hypertrophy, and other conditions have been formulated. Some enthusiasts in this field have considered data so acquired to be more reliable than conflicting evidence obtained from conventional limb and multiple precordial leads. This truly amazing situation denies the truth of basic time-tested concepts of electrocardiographic interpretation and substitutes for them criteria that are supported by little except the fancy apparatus used to record the vectorcardiograms and the enthusiasm of the physicians who operate the machines.

Vectrocardiograms can be no more accurate or informative than are the leads employed to derive them; yet many vectorcardiographers have not examined the leads they use to decide whether they provide satisfactory transverse, vertical, and sagittal components of the mean cardiac electromotive forces. If the leads fail to meet this requirement, their combination cannot give accurate vectorcardiograms. Two quite different systems of leads have been used to take vectorcardiograms. Duchosal and Sulzer[4] introduced the so-called cube arrangement, which has been used in modified form by Grishman and associates[8] and others, while Burch and associates[5] have used the equilateral tetrahedron as the basis for their leads. In the latter system, Lead I is employed for the transverse component, AVF (or VF) for the vertical component, and a unipolar lead in the back behind the heart (VB) for the sagittal component.

The lead field described by McFee and Johnston[9] provides a tool to determine the behavior of leads of all kinds. When this method of analysis is applied to the leads used to obtain vectorcardiograms, it is clear that, of those employed with the tetrahedron system, only the vertical component, AVF, is satisfactory. Lead I gives only a fairly accurate transverse component but may be corrected easily by a simple technique suggested by McFee. VB does not provide a satisfactory sagittal lead, and this can only be obtained by the use of multiple small electrodes distributed in a grid arrangement over the precordium and posterior chest wall behind the heart, as described by McFee and Johnston.[9]

When the leads used in the cube system are analyzed by a study of their lead fields, it is clear that none of these leads give accurate components of the cardiac electromotive forces, and this can only mean that vectorcardiograms taken with them are subject to considerable error. Nevertheless, most of the workers who have expressed the view that their vectorcardiograms are more reliable and provide data not present in conventional electrocardiograms use this technique.

This discussion raises a very important question. Can all the voltages produced throughout the heart be completely represented by a single equivalent dipole located within this organ? Only if this is possible can vectorcardiograms that provide all the information available in multiple conventional electrocardiograms be recorded. This problem, basic as it is, has been given little consideration, and only recently has it been realized that the proper choice of leads or lead systems to obtain the transverse, vertical, and sagittal components of this ideal equivalent dipole may be essential to its satisfactory solution.

The lead field concept points out, in a way that is easily understood, how leads must be arranged to obtain accurate transverse, vertical, and sagittal components of the mean cardiac electromotive forces in the simplest fashion. It is perhaps significant that combinations of leads varying from the relatively simple ones employed to obtain the vertical and transverse components (AVF and corrected Lead I, respectively) to the more complicated multiple electrode grid arrangement necessary to derive the sagittal component are required if systems providing lead fields ideal for vectrocardiography are to be secured. It is logical that more or less complicated lead systems rather than the cube or tetrahedron arrangements, that employ only four electrodes, should be required to obtain components that are accurate and represent all electromotive forces generated in the heart.

Other types of leads like those proposed by Burger, van Milaan, and den Boer[10] may be used to obtain vectorcardiograms, provided the leads have previously been analyzed, as these authors have done, so that their lead vectors are known and the coefficients necessary to correct the "raw" lead voltages to obtain the desired orthogonal components are available. Unfortunately such analyses must be done on models or cadavers, and many factors may enter to make the procedure somewhat inaccurate.

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It seems likely, if proper leads are employed, that vectorcardiograms can be recorded which contain essentially all the information that can be gleaned from many conventional electrocardiograms. The question is not, therefore, whether these "ideal" vectorcardiograms are superior to conventional tracings or the reverse, but rather whether the usual or the vector type of presentation is desired. If the technique for obtaining the required vectorcardiographic leads and the apparatus for taking vectorcardiograms were simple and inexpensive, it is quite possible that vectorcardiograms (except for a few conventional tracings to be used for the measurement of some important intervals and in the diagnosis of some of the arrhythmias) might largely replace ordinary electrocardiograms. Unfortunately, neither of these premises is true, since the method to obtain satisfactory leads for the vectorcardiographic components is just as complicated as that involved in the registration of the usual twelve routine electrocardiograms, and the equipment required for vectorcardiography is far more elaborate than is the ordinary electrocardiograph. Technical improvements may, of course, alter the current situation, but for the present and the immediate future, vectorcardiographic representation of this kind seems to be a luxury for research groups in large medical centers.

A few words must be said about simpler methods, like those employed by Grant and associates,[6] for displaying conventional electrocardiograms in vectorial fashion. Ingenious techniques have been devised by these authors, Simonson,[11] Witham and Hamilton,[12] and others to depict the mean or certain instantaneous values of the QRS complexes or T waves by vectors, and there is no doubt that these schemes have helped many students and physicians to understand how findings in many different kinds of leads may be derived from electromotive forces arising in the heart. These methods are of considerable value in the teaching of electrocardiography, but since the vectors are derived from con-

ventional electrocardiograms by techniques that are often subject to considerable error, they not only contain no data not present in ordinary records, but may be so inaccurate that they are misleading. In my opinion, these methods should not be considered as a new tool for investigation.

This discussion of vectorcardiography is incomplete in many respects but is based largely on fundamental facts about which there cannot be great difference of opinion. The value of the lead field concept and its application in the study of vectorcardiographic leads may be unfamiliar to some but, in my opinion, this method has opened entire new vistas in our understanding of the behavior of all kinds of electrocardiographic leads and in the design of new and better ones. Vectorcardiography is one field of electrocardiography where application of the lead field idea has helped immeasurably.

FRANKLIN D. JOHNSTON

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EXCISION OF AORTIC ANEURYSMS

The treatment of aortic aneurysms by resection and reconstruction of aortic continuity, once thought to be so formidable as even to be denied consideration, has now become the method of choice. This involves the use of an old principle with new vigor and enthusiasm made possible by improvements in techniques of vascular surgery, anesthesia, and chemotherapy. Tuffier, in 1902, first suggested and unsuccessfully attempted the excision of a saccular aneurysm of the ascending aorta. This was done after he examined eight specimens in the Dupuytren Museum and demonstrated to his satisfaction that many saccular aneurysms of the ascending aorta have a narrow mouth which can be clamped, divided, and sutured. The abuse which Tuffier was given in the medical society is as much a commentary on his foresight as on the state of vascular surgery at the turn of the century.

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Tuffier's contribution lay dormant for almost half a century while occasional reports were made of success in the treatment of aortic aneurysm by endoaneurysmorrhaphy or ligation. Both methods carried a prohibitive risk unless the aneurysm had ruptured and death was imminent without treatment. In 1943 Harrison and Chandy first placed cellophane about an aneurysm in the hope that with subsequent contraction of the scar some constriction of the swelling would occur. This technique has since been widely used but with little effect upon the expected survival period and only slight effect upon symptoms related to aortic aneurysm. Blakemore and King refined a technique by which wire was fed into the aneurysm and developed an apparatus to permit controlled heating of the wire once it was inserted. Blakemore's results were the best reported at mid-century.

Successful excision of coarctation of the aorta by Gross and by Crafoord and the treatment of congenital cyanotic heart disease by Blalock gave tremendous impetus to vascular surgery and were responsible for the development and refinement of techniques, instruments, and anesthesia which made possible a direct attack upon aneurysms. Sporadic attempts at excision and rare successes were reported by several surgeons who were unexpectedly confronted with an aneurysm in attempting to remove a lesion initially diagnosed as a tumor. None advocated planned excision of aneurysms, except in patients with coarctation where collateral channels are present, until Cooley and DeBakey,[1] Dubost,[2] and Bahnson[3] advocated a direct attack and excision of the aneurysm and reported successful cases to substantiate the argument. For the first time the chance of a cure was great enough to justify a sizable operative procedure.

Aortic aneurysms of all types are in most instances amenable to excision. Those due to syphilis, and the uncommon traumatic or mycotic aneurysms, are usually saccular with a relatively narrow mouth. Although they occur most commonly in the thoracic aorta where cross-clamping of the aorta is possible for only a short period, the mouth of the aneurysm can usually be isolated, clamped,

and the aneurysm excised. Arteriosclerotic aneurysms, although commonly fusiform in nature, fortunately almost invariably arise in the terminal portion of the abdominal aorta, where the parent vessel may be clamped above and below, the aneurysm excised, and a graft used to reconstruct the lumen.

Of the two general types of aneurysms, those due to syphilis are likely to be more dangerous to the patient. Survival at the present time is improved with the use of modern drugs but, prior to this, the interval from onset of symptoms to death was significantly less than one year in a majority of the patients. Irrespective of the challenge to survival, patients with syphilitic, traumatic, or mycotic aneurysms are likely to have symptoms of pain or interference with function of the thoracic organs in close proximity to the aorta.

At operation, although the aneurysm itself is usually adherent to the adjacent structures and dissection is dangerous, the adjacent aorta is surprisingly free and may be easily mobilized sufficiently to allow clamping of the mouth of the aneurysm. In most instances, when the aneurysm is opened one can distinguish a discrete line between the badly diseased aneurysmal wall and the diseased but functionally adequate aorta. There is every reason to believe that, with adequate antibiotic treatment, the remaining aorta will function satisfactorily for many years. The tissue in the mouth of the aneurysm is usually tough and adequate for suture and closure of the aneurysmal mouth and has offered no serious technical problem.

Arteriosclerotic aneurysms are increasing in incidence both absolutely, because of increasing survival of the human being, and, relatively, because of the decreasing incidence of cardiovascular syphilis resulting from preventive and therapeutic measures. They almost invariably represent fusiform dilatations of the entire aorta distal to the visceral branches in the abdomen. Less than 5 per cent of them extend to involve the region of the renal arteries or above. The mechanism for such discrete localization and the reason for the prominence of the arteriosclerosis in the terminal aorta and the common iliac arteries are unknown. The common conception that these aneurysms involve the renal arteries is probably based upon a prevalent misconception of surface anatomy. Few persons recall that the aortic bifurcation is usually behind and frequently above the level of the umbilicus. Hence it is not surprising that most abdominal aortic aneurysms are palpable in the upper abdomen. Although the aorta and iliac arteries adjacent to such aneurysms contain such evidence of arteriosclerosis as calcified plaques, gross irregularity, and slight dilatation, they can be sutured to a graft to allow reconstruction. Since the aneurysms are so limited to the terminal portions of the aorta, there is no reason to believe that swelling will recur when the aneurysm is replaced by a graft from an individual in some instances fifty years junior to the recipient. Little or no danger is encountered by cross-clamping the abdominal aorta distal to the renal arteries provided one prevents dislodgment of clot from the aneurysm to the distal circulation or the occurrence of thrombosis in the stagnant iliac arteries during occlusion of these structures. Heparin can be instilled into the distal artery during the occlusion to prevent thrombosis; it is not required after operation.

Grafts used to reconstruct aortic continuity have been of many types, and the final selection of method of preservation is not yet made. The first ones were preserved by the method recommended by Carrel in the early years of this century. This idea was revived by Gross and his co-workers, who used homologous grafts to bridge large gaps in the treatment of coarctation of the aorta. In order to preserve such grafts for periods longer than a few weeks, later workers used grafts which were rapidly frozen and kept in the frozen state, or frozen and dried in a very low vacuum and kept in the dried state much as plasma is stored at room temperature. More recently Blakemore and Voorhees[4] have used synthetic fabrics for reconstruction of the aorta with satisfactory results. The use of a fabric has many advantages, not the least of which is the easy procurability and absolute sterility. Since there is no longer any doubt that the homograft is a dead structure or dies soon after implantation, the use of a totally inert material such as a synthetic fabric seems a logical step. Various fabrics, weaves, and means of fabrication are being investigated by several groups of workers.

Operative mortality currently is in the neighborhood of 25 per cent[5] but can obviously be lowered by judicious selection of patients with more regard to risk than possible benefit. There seems little question about the advisability of operation for syphilitic aneurysms, which are usually thoracic, since the two-year survival period in a large group of nonoperated cases reported by Kampmaier was less than 3 per cent. In addition, such lesions usually occur in younger individuals, prior to the age of 60, in whom the effects of aging are not so prominent. Arteriosclerotic aneurysms occur in older individuals in whom disease due to arteriosclerosis is a constant threat. Despite this threat, the risk of rupture of the arteriosclerotic aneurysm within one year is greater than the risk of operation.[6] In selection of patients, then, for operation, age is less of a determinant than the patient's desire and ability to undergo a sizable procedure in order to prolong his survival. A number of patients have been treated in their seventies.

There are still many problems remaining in the management of aortic aneurysm. These include the development of suitable techniques for treatment of the fusiform aneurysm of the proximal aorta, and especially the ascending arch, where cross-clamping is not possible. Shunts of various types have been used about the aortic arch, and hypothermia has been employed by DeBakey and Cooley to permit a longer interruption of the circulation. Further work upon various graft replacements and selection of the most satisfactory type remain to be done. Further experience will undoubtedly improve methods of handling elderly patients who undergo major operative procedures. In spite of these weaknesses in our surgical armamentarium, many patients who were formerly watched with doleful sympathy may now be restored to a brighter and normal life expectancy.

HENRY T. BAHNSON

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CHRONIC DISEASE AND THE BEHAVIORAL SCIENCES

We need all the help we can get if the many problems of chronic disease are to be solved. Fortunately, the increasing numbers of health workers who are attacking these problems are not alone in their efforts. Social workers and various consumer groups are deeply concerned, and many stand ready to help plan for wider use of new knowledge as it becomes available. Of even greater importance from the standpoint of research are the social scientists working both independently and in cooperation with health workers on problems relating to long-term illness.

These cooperative activities are much more widespread than is generally realized. For example, activities in the behavioral sciences throughout an entire university (Harvard)[1] were studied recently. To the surprise of all concerned, the survey showed that in this university's school of public health, medical and dental schools, and the associated teaching hospitals there were more than 100 on-going projects each of which involved the participation of one or more social scientists and which together had an annual budget of 1 million dollars. Although not all of these projects related to chronic disease, a great many of them did.

The subcommittee which worked on the health aspects of this study listed a number of areas likely to be of interest to both health workers and social (or behavioral) scientists. The areas overlap somewhat, and they are obviously not complete. The following list gives the areas considered to be of mutual interest, with a few examples of recent work going on in several of them:

1. *Reactions to Stress.*—Stress situations are well recognized as at least one of the multiple etiological factors in certain types of chronic illness. Simmons and Wolff,[2] in a fine example of social scientist–physician collaboration, discussed some of the mechanisms by which social stress may lead to disease. Saying "Now we can begin to know the price we pay in illness for a given way of life," they described the stresses the individual may have to endure in the process of socialization (the "bringing-up" process) and from the frictions produced by his often having to enact a set of seemingly incompatible roles. The "sources of the dynamics directing and limiting the adaptations that a person makes to his life situations" are categorized as (1) the biologic capacities with which he is genetically endowed at birth; (2) the actual physical environment to which he reacts as an organism; (3) the society to which he reacts as a group member; and (4) the culture to which he reacts as a person or personality. "The stress accruing from a situation is based in large part on the way the affected subject perceives it" so that at the present time extended life-history studies may be the most productive approach.

It is in the study of reactions to stress that mental health workers and social scientists find numerous points of contact with those concerned with psychosomatic medicine, or psychosocial medicine as Halliday[3] has described it in Britain.

2. *Sex, Reproduction, and Population Problems.*—The proportion of aged persons determines to a considerable degree the amount of chronic illness that can be found in a population at any one time (prevalence) and the new cases appearing within a given period of time (incidence). Thoroughgoing and continuing analysis of population trends, mobility, and similar considerations are of great importance.

3. *Child Development.*—Evidence accumulating from different cultures points to a strong correlation between child-rearing practices and the attitudes which adults later have about disease and healing.[4]

4. *Adult Personality.*—There is a recognized interdependence of certain personality factors and certain diseases, but much additional study is needed before the relationship can be sorted out successfully. It may be that personality and the capacity to endure pain can be profitably studied further.

5. *Gerontology.*—Older people in a culture which is changing as rapidly as is that of the United States have many problems, as Simmons[5] stated succinctly: "In the long and steady strides of a social order the aged find themselves fixed and favored in position and performance, but when conditions become unstable and the rate of change reaches a galloping pace the more youthful find opportunities in their favor and may become much earlier seated in the saddle." As one might imagine, there is a rapidly expanding literature on the problems of retirement.

6. *Social and Geographic Distribution of Factors Influencing Health.*—The manifold effects of climate, altitude, and other atmospheric conditions on many types of chronic disease are well known. Further studies are urgently needed to define more clearly such influences as urbanization and overcrowded living conditions and to explain the peculiar geographic islands where certain diseases are or are not found. Here are further opportunities for the epidemiologic approach to noncommunicable disease which Gordon, Clark,[6] and others have already begun to apply with considerable success, and which is related to much of the investigative work in social medicine in Britain.

7. *Motivation.*—Motivation of the patient is a most powerful determinant of the results of efforts to promote health, to apply specific protective measures for disease prevention, to make early diagnosis and institute prompt treatment, to limit disability, and to carry out successful rehabilitation. Strong motivation is needed to win the fight against chronic disease. Crampton[7] said, "In geriatrics we must remember that we turn over the management of the man to the man himself," and Stieglitz[8] noted that "the handicapped person will not exert himself toward rehabilitation if there is no place in society where he may find the satisfaction of usefulness."

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A conference on preventing chronic disease, in 1951,[9] pointed out that studies were needed to determine "what will influence people to believe that chronic disease is not necessarily hopeless"; "to lead the kind of life that reduces the danger of acquiring a chronic disease"; "to seek early detection"; "what will influence those who have a chronic disease to make the best possible adjustment to it"; and "what will influence the professions to give as much interest and attention to chronic disease as they now give to acute illness."

8. *Learning.*—The learning process, about which not nearly enough is yet known, is nevertheless the basis for our highly important health education work in chronic disease control programs. We have just scratched the surface of evaluating health education efforts. There is evidence that group learning, like group psychotherapy, may deserve a larger part in patient education than it now plays.

9. *The Roles of the Health Worker and of the Patient.*—The roles in which the physician sees himself and those in which the patient sees him are not always the same. Yet if the physician-patient relationship is to be constructive there must be a high degree of congruency in the perceptions which patient and physician have of each other's roles. Parsons[10] and others have done much to clarify the customary roles related to dealing with illness in the United States, and many studies elsewhere have shown how variable this situation may be. Saunders[11] has recently described the approach to illness made by the Spanish-American and how the role of the scientific physician in this system differs from the one to which most physicians in the United States are accustomed.

Havighurst[12] pointed up the importance of "role flexibility" in retirement, and his idea is applicable to many chronic disease situations whether or not they are complicated by aging. He said, "Living a social role means meeting community expectations. Meeting social expectations usually brings both social approval and personal satisfaction. . . . The ordinary person has the opportunity to fill a variety of social roles—parent, homemaker, husband or wife, son or daughter, member of a kinship group, member of an informal friendship group, club member, worker, church member, citizen, user of leisure time. . . . From about 50 to about 75 he is deprived of several social roles—grows discontented unless he is able to compensate for this by increasing activity in other roles or by the developing of new ones; that is by role flexibility. . . . How does a person achieve role flexibility? Probably the best assurance of role flexibility in later years is a reasonably successful experience in a variety of roles during the middle years."

10. *The Hospital as a Social System.*—The Harvard report[1] contained this statement: "We cannot study the effectiveness of hospitals and other health institutions solely by studying individuals with disease. We must study the therapeutic institution itself and its relation to the community. Also, each group of individuals brought together by a common role, working or being treated in a hospital, has a specific effect on other groups and on individual patients. Knowledge of these interrelations may greatly improve the effectiveness of our

health and medical programs. Our mental hospitals are a major economic burden. The study of these hospitals in particular may rapidly alter our operation of them."

11. *The Determinants of Response to Therapy.*—The Faculty Committee[1] raised this question: "If two patients appear to have the same illness, why does one get well and the other not? The determining factors may be of many kinds, and this seems an important field for interdisciplinary research. Rehabilitation of those who have been injured, diseased, or isolated by hospitalization is a subordinate but economically important part of our therapeutic activities that needs particular study" with regard to varying responses to therapy.

12. *Social Class and Health.*—Numerous morbidity studies have shown the importance of social class in the incidence of various chronic diseases, and mortality studies in the United Kingdom, where death certificates indicate the social class of the decedent, have confirmed this difference.

Koos[13] studied a small community included within the area of the Rochester, New York, regional plan for hospital services, to determine "what the people thought and did about their health." He found sharp differences between the three social classes (according to occupation) in their ways of looking at disease and their customary methods of dealing with it. His study led to the conclusion that "behavior regarding health and illness cannot be explained in terms of culture pattern or group pressure or cost or level of education alone, but is, rather, the result of the action of a complex of these."

13. *Decision-making Exemplified in Public Health Problems.*—Chronic disease is so likely to exhaust the financial resources of the individual and the family affected that it quite frequently demands some type of community decision and subsequent action to help meet the need. Recent years have seen numerous community studies and action programs much too numerous to mention here. Perhaps the most significant community development was the creation of the Commission on Chronic Illness growing out of the experience of four professional societies working together on certain phases of the problem. A good beginning has been made in stating the principles of graded physical facilities and of regional organization for dealing with chronic disease (and other disease as well), but this is only a beginning. We must find ways of measuring the effects on legislation and social policy of increasing numbers of those with some type of chronic disease among the voting population.

14. *Culture Change Exemplified in Efforts in Health Education.*—Many of our ways of dealing with chronic disease are so firmly embedded in the patterns of our culture that changes may be brought about only with a good deal of difficulty, and sometimes with unexpected repercussions. As a cultural anthropologist assessing the United States technical assistance health programs in Latin America, Foster[14] said, "Knowledge of people is just as important in many aspects of a public health program as is knowledge of medical science . . . cultures are integrated functional wholes. Public health programs should be planned and analyzed in relationship to, and as one aspect of, these wholes. . . . There are definite, though imperfectly understood, rules of human behavior

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which govern the processes whereby changes are brought about in culture. Specifically, popular resistance to public health programs can be scientifically studied, and methods can be developed whereby these resistances can be greatly reduced."

Even in the United States many people, especially in the lower income levels, resort to quackery, cultists, various forms of folk medicine, and home remedies when faced with chronic disease problems. Actually, the job that we have is not simply that of providing modern health services where no service of any kind was available before. It is not a job of filling a vacuum that we have in most instances, but rather one of displacing inferior methods of dealing with disease by introducing the allopathic approach which seeks the good in all methods of treatment.

15. *Intergroup Communication Problems.*—Before scientific knowledge is translated into appropriate public action there are many hurdles to be got over. There are semantic questions, technical "jargon," logic, illiteracy, problems of perception which sometimes make us see "what isn't there." Social psychologists are making important contributions in this area, with studies of the dynamics of groups and the use of various mass communication media.

16. *The Economics of Health and Disease.*—There is an abundance of literature on medical economics since this area intrigues social scientists, health workers, and organized consumer groups. Unfortunately, we have so far made too little progress in applying the principles of prepayment in medical care of chronic disease. There are some instances where attempts to do so are being made, and they should be carefully watched. Our prepayment plans, except for the few that provide a comprehensive type of care, make no serious attempt to provide the so-called preventive or early diagnostic services. Some hold that since such preventive services should be used by everyone they are not really insurable, but others question such statements. In any case, this is a highly important area of study.

17. *The Organization and Administration of Health Programs.*—The considerable body of knowledge of administration in other fields, although much of it is probably applicable to health work, has as yet been only partly applied to present medical problems.

Here, then, we have a number of promising areas in which collaborative investigation between health workers and behavioral scientists promises to be profitable. They seem well worth exploring.

HUGH R. LEAVELL

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Book Reviews

DIAGNOSTIC ADVANCES IN GASTROINTESTINAL ROENTGENOLOGY. By Arthur J. Bendick, M.D. Pp. 144, with 75 illustrations; indexed. New York, 1954, Grune & Stratton, Inc. Price $6.00.

This book is a rather brief personalized account of how the author performs roentgenologic studies of the gastrointestinal tract. The reader is aware that Dr. Bendick is indeed a busy radiologist in a large metropolis who divides his time between private and hospital practice.

A favorite device is the "club soda" technique in which a double contrast effect is gained by the use of barium and carbonated water. According to the author, the patient receives two teaspoonsful of a creamy barium mixture and mucosal films are obtained. A small bottle of club soda is then given in order to distend the esophagus or stomach with carbon dioxide gas. Among the indications for the use of this method are: (1) ulcers in the pyloric and postbulbar regions, (2) steerhorn or horizontal stomachs, (3) pyloric obstruction, (4) the study of the stomach after surgical procedures, (5) detection of small neoplasms, (6) outlining the extent of neoplasms.

The sections of the gastrointestinal tract are taken in sequence, and a brief discussion of certain diagnostic entities encountered in the gastrointestinal tract is appended. Because of its personal and sometimes partisan approach, the book should be perused quickly more for its general flavor rather than studied thoroughly as one might read a complete, dispassionate textbook.

DAVID M. GOULD

THE MEDICAL CARE OF THE AGED AND CHRONICALLY ILL. By Freddy Homburger. Pp. 253, with 6 figures; indexed. Boston, 1955, Little, Brown & Company. Price $5.75.

This slender volume of 250 pages carries an impressive title and an equally imposing subtitle: "With Particular Emphasis on Degenerative Disorders, Advanced Cancer and Other As Yet Incurable Diseases." The author, who has a distinguished reputation in the field of cancer research, has planned his book as "a practical guide to the physician who is anxious to apply to his chronic patient all that modern science has to offer to date, in order to minimize suffering and to control as yet incurable conditions."

A glance at the table of contents will indicate why this worthy objective has been incompletely achieved. The opening chapter on the role of the modern physician in the management of chronic illness is followed by chapters on osteoporosis, arthritis, malnutrition and debilitation, management of advanced cancer, management of hemiplegia, management of paraplegia, management of distressing complications of chronic illness, including urinary complications, gastrointestinal complications, complications originating in the central nervous system, as well as bed and pressure sores, concluding with nursing problems in chronic illness. The great area of cardiovascular disorders is not included at all. Infectious diseases and diseases of the mind are treated only in passing. While part of the opening chapter is devoted to "preventive geriatrics," the author emphasizes only periodic physical check-ups. The reader has difficulty in finding any advice as to the management of the aged person who is not suffering from one of the specified long-term maladies. Also missing is any reference to the altered reactions to disease of the aging body. As to the problems of the mental health of the patient and his family "the physician must rely on his judgment, his philosophy and his heart."

The strong point of this volume, in the opinion of the reviewer, is the steady insistence on the value of the doctor-patient relationship and the practitioner's obligation to know his patients intimately in order to treat them as individuals. In discussing the management of colostomies the author urges that "the physician maintain a sufficiently close relationship with these patients for them to discuss with him their problems, fears and anxieties. He may thus contribute to a better state of mind and mental balance, and, as a result, a more smoothly functioning colostomy."

The section on chemotherapy of advanced cancer is covered thoroughly and in the authoritative manner of one who is at home in this field. The writer is conservative in his evaluations of different methods, but expresses optimism for future developments along this line of approach.

On the whole this is an uneven disappointing treatment of a tremendously important field to which more and more constructive effort is steadily being applied. The beginner, whether practitioner or student, will best serve his own purposes by going to textbooks covering special fields, such as rehabilitation, and by basing his reading on one of several bibliographies that have been prepared.

This review cannot be concluded without a brief comment on the prominent place occupied in this book by the late Raoul Dufy, the distinguished French artist, who figures in the dedication, in an appreciative note placed opposite the table of contents and in some six pen-and-ink sketches of hospital life. One of these, showing the author at the artist's bedside, serves as frontispiece. However interesting these may be as examples of the artist's work under the influence of cortisone, or as mementoes of a distinguished patient, they seem out of place in a medical work since they have no direct bearing on the text, and add nothing to the value of the book as a source of reliable information in the field of long-term illness.

F. D. Zeman

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HOW TO HELP OLDER PEOPLE: A GUIDE FOR YOU AND YOUR FAMILY. By Julietta K. Arthur. Pp. 500; indexed. New York, 1954, J. B. Lippincott Company. Price $4.95.

In the past, the problems of the three-generation family were minimal. In a rural environment, grandpa or grandma could continue to live in the large house with their children and grandchildren without difficulty. Today, with the shift toward urbanization and industrialization, and with smaller apartments and houses, the problems of living for both parents and their middle-aged children have become much more difficult. Furthermore, older people have changes. Whistler's mother, with folded hands, no longer serves as the prototype of aging people. Today, the aging want to remain active in community and family life, but our social structure is likely forcibly to remove the mainstay of their independence; namely, employment. At the same time, middle-aged children still feel a sense of responsibility for their parents but may be denied the means by which they can meet the material and emotional needs of their older family members. Often they are unaware of the emotional needs of this new breed of elderly relative. It is to these problems that Mrs. Arthur has devoted her book, with the general theme of prevention of tensions, frustrations, heartaches, and sense of guilt that are so often a part of present-day living among three- or four-generation families. It is a book organized around specific problems of finances, work and retirement, health, living arrangements, and activities for older people. It offers practical suggestions for the solution of these problems in a most readable style. Mrs. Arthur is to be congratulated on her success in presenting the essence of much technical research in understandable form, with specific illustrative examples that make the book live (although some may quibble with the details of some of the generalizations). The over-all picture of aging which she gives is accurate. Her emphasis on the individuality of aging and her insistence that "old age is not a disease" are especially commendable. The book deals forthrightly with the problems of terminal illness and senile mental deterioration on the premise that to be forewarned is forearmed. In this chapter, as in all others, practical suggestions are given for meeting these problems when they arise. The book will assist every family in planning for, and with, its older members; where to live, how to determine whether employment is desirable, how to go about finding a job, how to choose a physician, how to select and judge a nursing home or other institution, whom to see when expert counseling is needed, where to go for social experiences, and how to develop satisfying leisure time activities. These questions, and many others, are discussed in a practical fashion. One important aspect of the book is the appendix which provides a directory of services available to assist in the solution of specific problems. This aspect of the book makes it a valuable reference not only to the individual with a problem, but to professional workers as well.

Mrs. Arthur has produced a volume that should be as available to every family as the standard books on child care. It is a book for the aging as well as the aged.

N. W. Shock